VOLUME 50 NUMBER 1 JULY, 1960

AMERICAN JOURNAL
OF
OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON

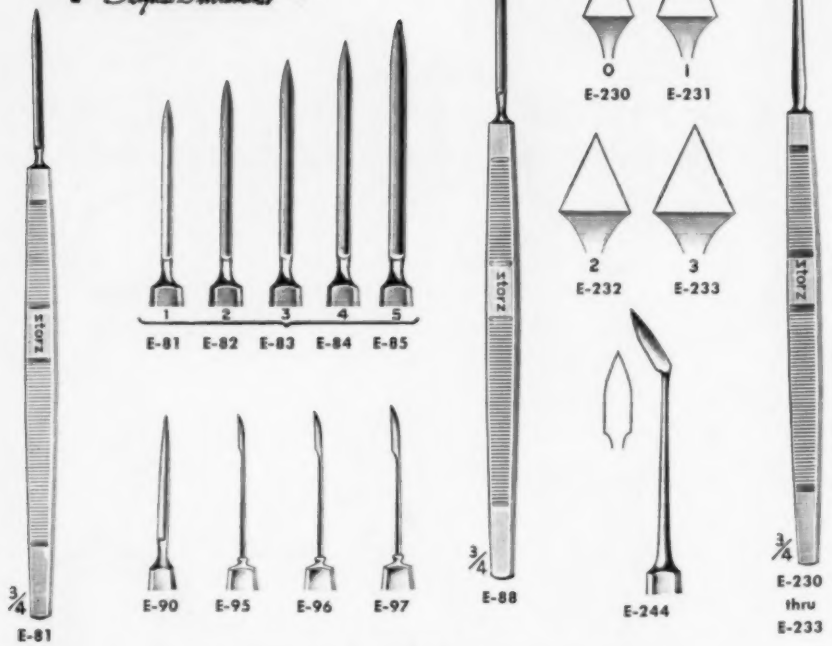
CONTENTS

For a complete table of contents see page xxxix

Publication office: Curtis Reed Plaza, Menasha, Wisconsin

Subscription price in United States twelve dollars yearly. In Canada and foreign countries fourteen dollars. Published monthly by the Ophthalmic Publishing Company. Subscription and Advertising Office: 664 North Michigan Avenue, Chicago 11, Illinois. Second class postage has been paid at the post office at Menasha, Wisconsin. Printed in U.S.A.

storz
Surgical Instruments



E-81
thru
E-85

STORZ DUREDGE STAINLESS STEEL EYE KNIVES

Made of
Special Alloy Cutlery Stainless Steel

The grain structure of this alloy steel is dense and it will hold a keen penetrating edge. Improved methods in hardening, tempering and honing plus this new Stainless Alloy Steel have resulted in a superior knife.

E- 81*	Cataract Knife, VON GRAEFE: 25mm x 1.5 mm.	$10.00
E- 82*	Cataract Knife, VON GRAEFE: 27mm x 1.7mm.	10.00
E- 83*	Cataract Knife, VON GRAEFE: 30mm x 2mm.	10.00
E- 84*	Cataract Knife, VON GRAEFE: 33mm x 2.3mm.	10.00
E- 85*	Cataract Knife, VON GRAEFE: 35mm x 2.5mm.	10.00
E- 88*	Cataract Knife, Duredge: a straight back medium size cataract knife with wafer thin blade for extreme sharpness and easy penetration.	15.00
E- 90*	Knife, Discision, WHEELER: 1mm x 18mm blade.	12.50
E- 95*	Knife Needle, ZIEGLER: 5mm.	11.50
E- 96*	Knife Needle, ZIEGLER: 6mm.	11.50
E- 97*	Knife Needle, ZIEGLER: 7mm.	11.50

STORZ DUREDGE Stainless Steel Keratomes

E-230*	Keratome, JAEGER: size 0, angled, 8mm x 9½mm.	$11.50
E-231*	Keratome, JAEGER: size 1, angled, 9½mm x 11mm.	11.50
E-232*	Keratome, JAEGER: size 2, angled, 11mm x 12½mm.	11.50
E-233*	Keratome, JAEGER: size 3, angled, 12½mm x 14mm.	11.50
E-244*	Keratome, CASTROVIEJO: blade 13mm x 4mm, parallel portion of blade is not sharp.	12.50

Storz Duredge Stainless Steel and Duredge Carbon Steel cataract knives and keratomes are not imported, they are made only in our factory in St. Louis. All of our re-sharpening is also done in our own factory by skilled instrument makers.
We do not utilize outside facilities for re-sharpening any eye knives.

* Designates STAINLESS STEEL.

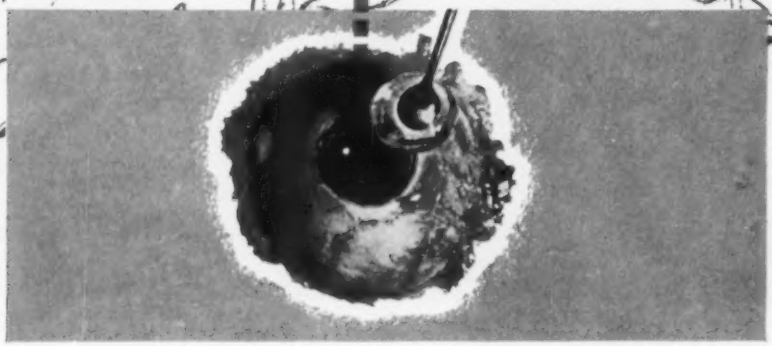
STORZ INSTRUMENT COMPANY • 4570 Audubon Avenue, Saint Louis 10, Mo.

New York Showroom: 157 E. 64th St. at Lexington Ave.

ALPHA CHYMAR®

alpha chymotrypsin

TAKES "THE MOMENT OF ANXIETY" OUT OF CATARACT SURGERY[1]



ALPHA CHYMAR—lyophilized crystallized chymotrypsin—loosens the zonule fibers of the lens within minutes, and thus "can serve to relieve that moment of anxiety for the cataract surgeon when he meets up with a tough zonula. [ALPHA CHYMAR] helped to prevent the complications of capsule rupture and of undue zonular traction on structures of the inner eye."[1]

Data obtained in a double-blind study indicate "in an objective manner that alpha chymotrypsin definitely facilitates cataract extraction"[2] thus further confirming its value as a new adjunct in cataract surgery.[3,4,5,6]

Specifically packaged for zonule lysis in lens extraction, ALPHA CHYMAR is available in cartons of 5 packages. Each package contains a 5 cc. vial of lyophilized ALPHA CHYMAR and a 10 cc. vial of ALPHA CHYMAR DILUENT (Sodium Chloride Injection, USP).

1. Thorpe, H. E.: Am. J. Ophth. *49*:531-547 (Mar.) 1960. 2. Schwartz, B., *et al.*: Tr. Am. Acad. Ophth. & Otol. *64*:46-54 (Jan.-Feb.) 1960. 3. Cogan, J. E. H.: Proc. Roy. Soc. Med. *51*:927, 1958. 4. Jenkins, B. H.: J.M.A. Georgia *45*:431, 1956. 5. Raiford, M. B.: J.M.A. Georgia *48*:163, 1959. 6. Rizzuti, A. B.: Arch. Ophth. *61*:135, 1959.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS

Armour Means Protection

Acute conjunctivitis[1] before treatment, showing engorged irregular superficial vessels

NOW...the true solution for fast anti-inflammatory response and no irritating steroid particles

- mg. for mg. the most active steroid topically—up to 40 times the potency of hydrocortisone
- optimal not minimal steroid concentration in true solution for peak effectiveness . . . maximal contact at the site of the lesion
- quick-acting broad antimicrobial activity when infection threatens recovery
- superior patient comfort—no stinging, no irritating particles, bland carrier

1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.

4 days after treatment ACTUAL CLINICAL PHOTOGRAPHS

OPHTHALMIC SOLUTION

NeoDecadron*

DEXAMETHASONE 21-PHOSPHATE—NEOMYCIN SULFATE

INDICATIONS: Trauma—mechanical, chemical or thermal; conjunctival, corneal, or uveal tract inflammation involving the anterior segment; allergy; blepharitis.

DOSAGE: NeoDECADRON Ophthalmic Solution (0.1%)—One drop 4-6 times daily.
NeoDECADRON Ophthalmic Ointment (0.05%)—Applied 3-4 times daily.

In severe or sight-threatening conditions, the frequency of administration may be increased. Systemic therapy with DECADRON Tablets may be prescribed adjunctively.

PRECAUTION: Steroid therapy should never be employed in the presence of tuberculosis or herpes simplex.

Additional information is available to physicians on request.

*NeoDECADRON and DECADRON are trademarks of Merck & Co., Inc.

Product	Steroid Concentration	active ingredients: Dexamethasone 21-Phosphate (as the disodium salt)	active ingredients: Neomycin Sulfate	Supplied
NeoDECADRON Ophthalmic Solution	0.1%	1 mg./cc.	5 mg./cc. (equivalent to 3.5 mg. neomycin base)	5 cc. (¼ oz.) sterile dropper-bottles
DECADRON Phosphate Ophthalmic Solution	0.1%	1 mg./cc.	—	5 cc. (¼ oz.) sterile dropper-bottles
NeoDECADRON Ophthalmic Ointment	0.05%	0.5 mg./Gm.	5 mg./Gm. (equivalent to 3.5 mg. neomycin base)	3.5 Gm. (⅛ oz.) tubes
DECADRON Phosphate Ophthalmic Ointment	0.05%	0.5 mg./Gm.	—	3.5 Gm. (⅛ oz.) tubes

MSD MERCK SHARP & DOHME
Division of Merck & Co., Inc. • Philadelphia 1, Pa.

REFLECTION ON
CORTICOTHERAPY:

The clinical aim, following immediate suppression of disease symptoms, is to maintain the patient symptom-free... with minimal side effects.

The logical course is to select the steroid with the best ratio of desired effects to undesired effects:

the corticosteroid that hits the disease, but spares the patient

Medrol*

Upjohn THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

*TRADEMARK, REG. U. S. PAT. OFF.—METHYLPREDNISOLONE, UPJOHN

Barnes-Hind WETTING SOLUTION

Sterile, non-irritating... optimal re-sterilizing[1] activity.

Formulated for freedom from ocular burning and stinging, Barnes-Hind Wetting Solution cleans and wets in one action. It is sterile, non-irritating. Its prolonged wetting-out action lubricates lenses efficiently all day, promotes desired floating effect, makes longer wearing possible. Active ingredient, benzalkonium chloride 0.004%.

SOQUETTE® SOLUTION

For sterile, antiseptic lens storage.

Storage in Soquette Solution prevents natural oils and ocular sebaceous secretions from drying onto the lens surfaces, and prepares the lenses for optimal wetting action. Blurring and irritation caused by drying-out of lenses are eliminated. Effectively antiseptic[1] for greater safety. Active ingredients, chlorobutanol 0.3% and benzalkonium chloride 0.004%.

DEGEST®

Soothes, refreshes, and clears ocular tissues.

Sterile Degest promptly relieves inflammation of ocular epithelial tissues which may result from excessive lens wearing. Ordinarily this condition subsides slowly. Degest brings about quick subjective relief. It contains phenylephrine hydrochloride 0.2% in a mildly hypertonic vehicle, benzalkonium chloride 0.01% and sodium bisulfite 0.1% as preservatives.

Cotton-Tipped MINIMS®

(Sterile Fluorescein Sodium 2%)

Convenient, safe, sterile... no wastage

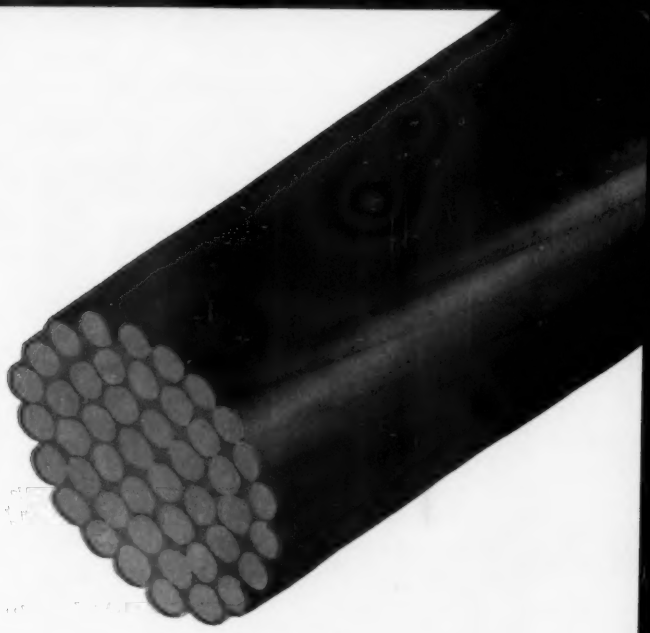
Each Minims unit is a sterile disposable applicator designed for single-patient use. Supplied in containers of 20 individually over-wrapped Minims units.
TECHNIQUE OF APPLICATION:
Remove the over-wrap and squeeze the contents of the unit into the sterile cotton tip. Apply to the lower lid or bulbar conjunctiva. Discard the unit.

EFFECTIVE AIDS

to successful contact lens fitting/wearing

[1] CLIFTON, C. E. AND HALL, N. C. "RE-STERILIZING ACTIVITY OF CERTAIN CONTACT LENS SOLUTIONS." CONTACTO, THE CONTACT LENS JOURNAL, 3:10, 301-2, 1959.

Manufactured by **BARNES-HIND** OPHTHALMIC PRODUCTS, INC., 895 KIFER ROAD, SUNNYVALE, CALIFORNIA. REGENT 6-5462

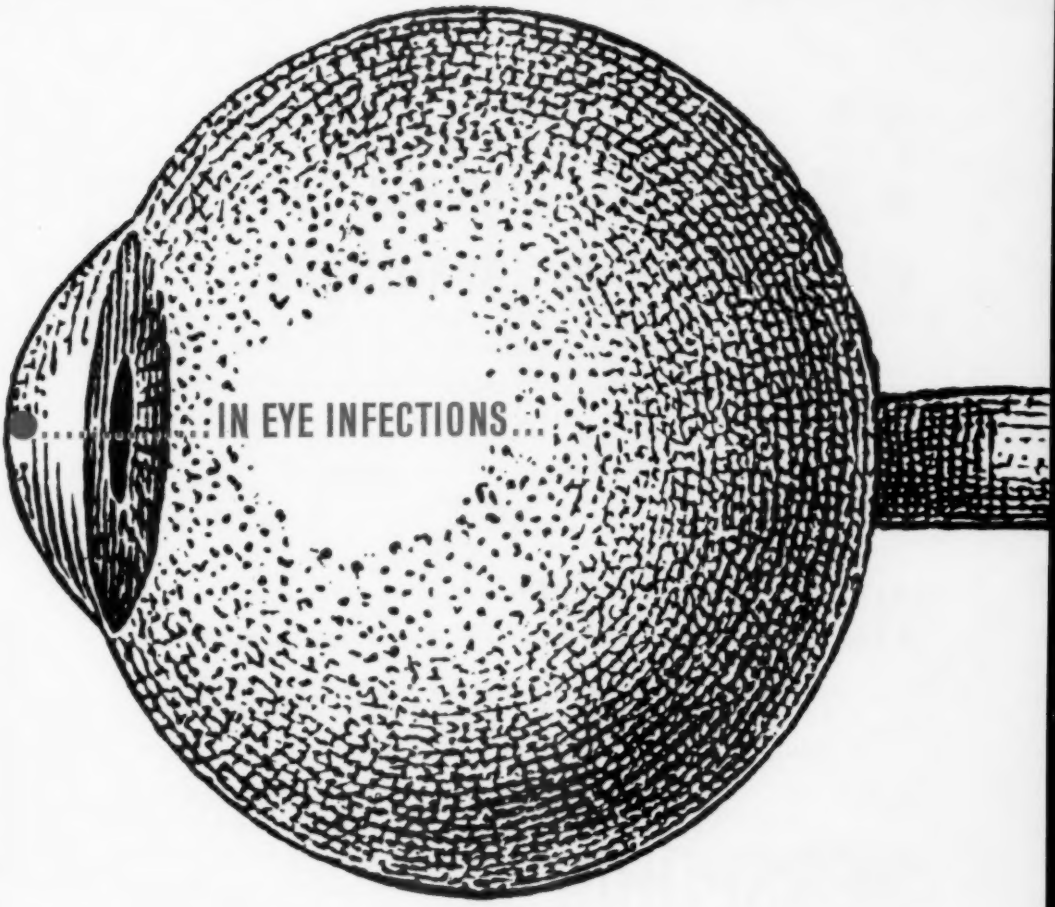


NEW MERSILENE® polyester fiber

ophthalmic needle sutures

Smoother, stronger, braided **MERSILENE** polyester fiber sutures reduce trauma, minimizing tissue reaction. Dyed green for maximum visibility, they're swaged to **ETHICON MICRO-POINT®** needles for the exacting requirements of ophthalmic surgery.

ETHICON®



QUICK AND EFFECTIVE CONTROL WITH

OPHTHOCORT®

CHLOROMYCETIN® (chloramphenicol, Parke-Davis) – polymyxin B – hydrocortisone ophthalmic ointment

In the treatment of ocular infections, OPHTHOCORT Ophthalmic Ointment offers these significant therapeutic benefits: Prompt antibacterial and anti-inflammatory action • Good results against gram-negative as well as gram-positive invaders • Steroid protection against inflammation, discomfort, and possible scarring of ocular tissues • Virtual absence of irritative or allergic properties

OPHTHOCORT is intended for the topical treatment of ocular inflammation complicated by infection. It is administered by local application two to four times daily, as required.

OPHTHOCORT Ophthalmic Ointment contains 1% CHLOROMYCETIN (chloramphenicol, Parke-Davis), 0.5% hydrocortisone acetate, and 5,000 units polymyxin B sulfate per Gm.; supplied in ⅛-oz. tubes.

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

20660

PARKE-DAVIS

WHEN YOU SEE

ocular trauma

OR INFLAMMATION

Chymar®

Buccal/Aqueous/Oil

systemic route to faster healing

controls inflammation, swelling and pain

hyphema—(traumatic and postoperative)
"Improvement with the use of Chymotrypsin (Chymar) noted in all cases within 24 hours."[1]

secondary inflammation
"Chymotrypsin definitely shortens the course of ophthalmic inflammations and hastens the absorption of blood in the tissues."[2]

vitreous hemorrhage
"Two of three cases in this group showed definite improvement within six weeks."[1]

effective anti-inflammatory enzyme

CHYMAR Buccal—Crystallized chymotrypsin in a tablet formulated for buccal absorption. Bottles of 24 tablets. Enzymatic activity, 10,000 Armour Units per tablet.

CHYMAR Aqueous—Solution of crystallized chymotrypsin in sodium chloride injection for intramuscular use. Vials of 5 cc. Enzymatic activity, 5000 Armour Units per cc.

CHYMAR—Suspension of crystallized chymotrypsin in oil for intramuscular injection. Vials of 5 cc. Enzymatic activity, 5000 Armour Units per cc.

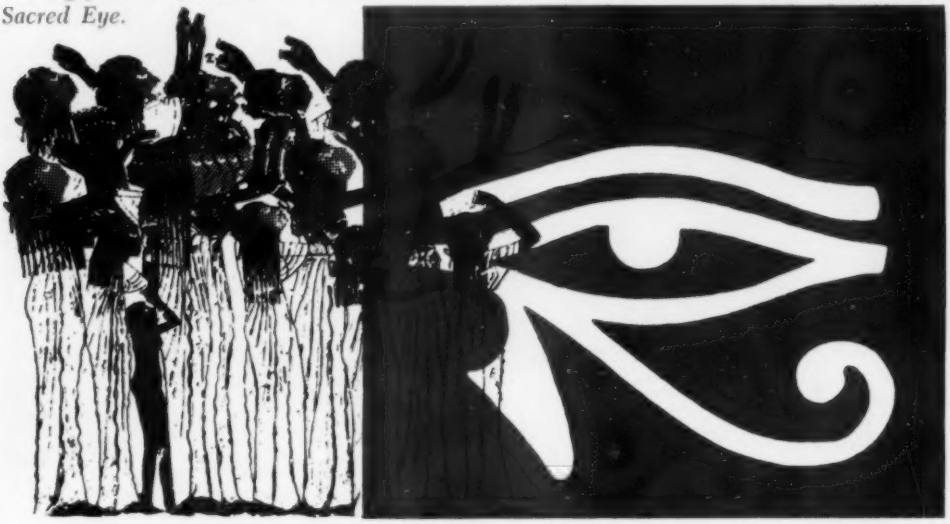
and for enzymatic zonule lysis *Alpha* CHYMAR

1. Jenkins B. H.: J. M. A. Georgia *45*:431 (Oct.) 1956
2. Fullgrabe, E. A.: Ann. New York Acad. Sc. *68*:193 (Aug. 30) 1957.

ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS
Armour Means Protection

CHYMAR

YESTERDAY... In ancient Egypt, when sight was threatened by the evil demons of disease, the patient sought relief by invoking the healing powers of UTCHAT—The Sacred Eye.



TODAY... IN SEVERE INFLAMMATORY AND ALLERGIC EYE DISEASE

new Prednefrin Forte® OPHTHALMIC SUSPENSION

PROVIDES UNEXCELLED EFFECTIVENESS FOR TOPICAL THERAPY

In many cases where other topical steriods have failed, PREDNEFRIN FORTE—the newest and most potent addition to the Prednefrin family—has demonstrated remarkable clinical effectiveness.[1]

PREDNEFRIN FORTE is specifically designed to treat the most severe anterior segment inflammatory disease effectively by virtue of its unique formula: prednisolone acetate *1.0%* for unexcelled counteraction of the disease process by its potent anti-inflammatory activity, plus . . . phenylephrine HCl .12% for rapid improvement of the eye's appearance and "feel" by its decongestant action.

PREDNEFRIN FORTE—presented in the special Allergan "solution-like" suspension—*offers new hope for saving sight whenever the functional integrity of the eye is threatened.*

TODAY—Whatever the degree of severity . . . whenever the diagnosis is ocular inflammation and/or allergy, you'll find a PREDNEFRIN specifically indicated.

SEVERITY	PREPARATION	INGREDIENT & STRENGTH Prednisolone	Phenylephrine
Mild	Prednefrin Ophthalmic Suspension	0.12%	0.12%
Moderate	Prednefrin S Ophthalmic Solution	0.2%	0.12%
Severe	Prednefrin Forte Ophthalmic Suspension	1.0%	0.12%

Indications: All Prednefrin formulations are indicated in inflammatory and/or allergic disorders of the eyelids, conjunctiva, cornea, sclera and uveal tract—the degree of severity should determine the therapeutic choice.

Dosage: 1 to 2 drops, two to four times daily. During the initial 24-48 hours, this dosage may be safely increased to 2 drops every hour.

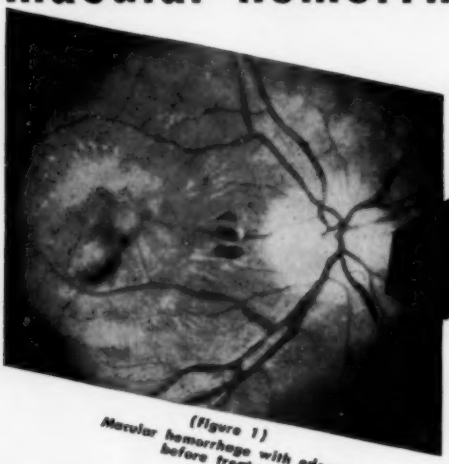
Caution: Prednisolone is contraindicated in herpes simplex. If infection is present, appropriate anti-infective therapy should be employed.

Supply: Each member of the Prednefrin family is available in 5 cc. plastic dropper bottles, on prescription only.

Reference: 1 Albaugh, C.H.: Personal communication, 1959.

ALLERGAN PHARMACEUTICALS, INC., *Los Angeles 17, California*

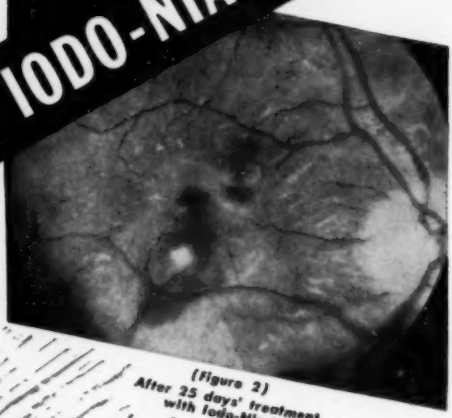
macular hemorrhages



(Figure 1)
Macular hemorrhage with edema, before treatment

respond to

IODO-NIACIN*



(Figure 2)
After 25 days' treatment with Iodo-Niacin

NO IODISM

Macular and retinal hemorrhages are satisfactorily absorbed after use of IODO-NIACIN[1]. The dosage used in this study was 1 tablet three times daily.

In cases of cerebral and generalized arteriosclerosis, IODO-NIACIN has been used with great benefit[2]. Full doses were given for a year or longer without any iodism or ill effects.

The formula of IODO-NIACIN Tablets contains potassium iodide 135 mg. (2¼ gr.) combined with niacinamide hydroiodide 25 mg. (⅜ gr.). IODO-NIACIN Ampuls 5 cc. are highly satisfactory for intramuscular or intravenous use[3].

Since the retina is intrinsically a part of the brain[4], hemorrhages in this region are indicative of a similar cerebral condition for which IODO-NIACIN is directly indicated.

IODO-NIACIN Tablets, slosol coated pink, are supplied in bottles of 100. Ampuls 5 cc. in boxes of 10.

1. *Am. J. Ophth.* 42:771, 1956.
2. *Am. J. Digest Dis.* 22:5, 1955.
3. *Med. Times* 84:741, 1956.
4. *Cecil's Textbook of Medicine*, 7th ed., 1947, p. 1598.

Cole
CHEMICAL COMPANY
3721-27 Laclede Ave.
St. Louis 8, Mo.

* U.S. Patent Pending

Write for professional samples and literature

Cole Chemical Company AJO-7
3721-27 Laclede Ave., St. Louis 8, Mo.
Gentlemen: Please send me professional literature and samples of IODO-NIACIN.
DOCTOR _____
STREET _____
CITY _____ STATE _____ ZONE _____

dynamic control of GLAUCOMA

IN DIAGNOSIS – By reducing corneal edema, DIAMOX facilitates examination and diagnosis in ophthalmologic disorders.

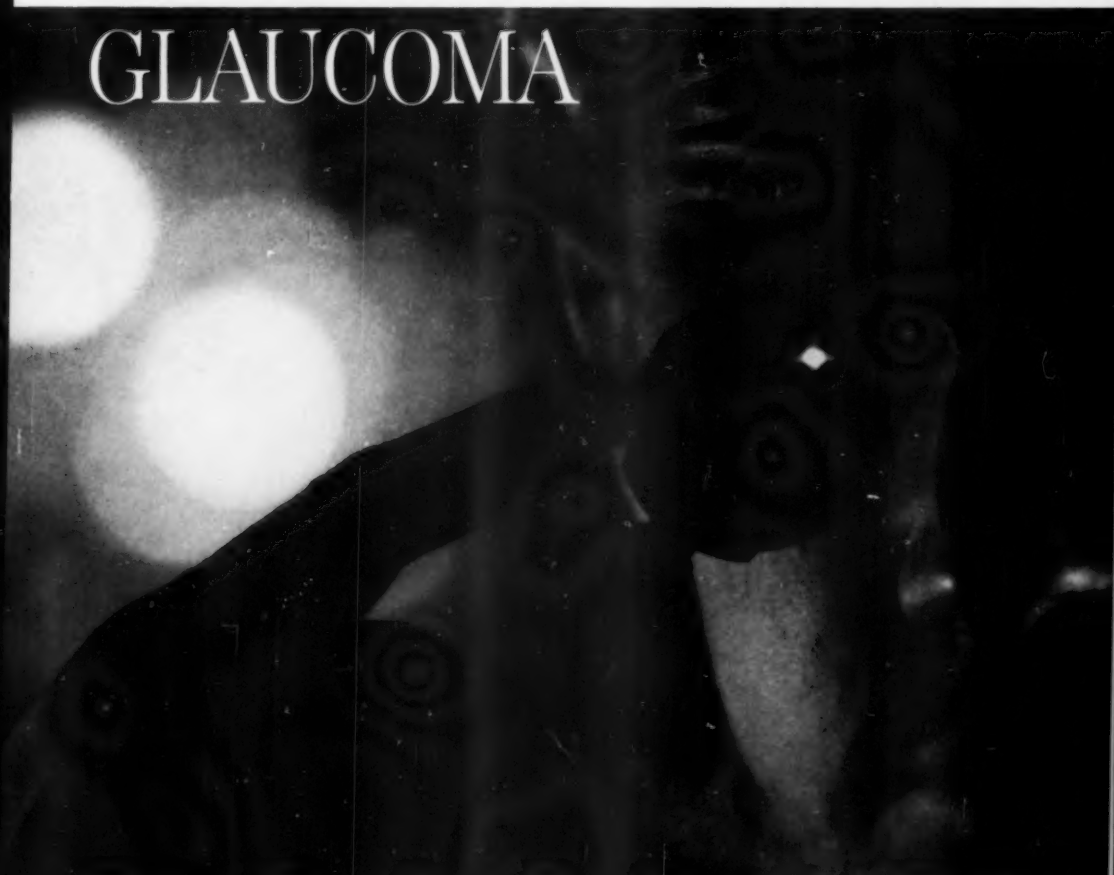
AS THERAPY – By lowering intraocular pressure, conservative therapy with DIAMOX can often reduce the need of surgical intervention in various glaucomatous conditions. Traumatic hyphemas, for example, can be resolved without cyclodiathermy puncture.[1]

PRE- AND POSTOPERATIVE CARE – Where surgery is required, tension is first reduced by DIAMOX and maintained after surgery to speed healing. Used with miotics, the synergistic action improves efficacy.[1]

Suggested DIAMOX dosage for glaucoma: 250 mg. every four hours. In severe glaucomatous crises, the intravenous form may provide quicker reduction of global pressure.

Supplied: Scored tablets of 250 mg., and Vials of 500 mg. for parenteral use.

1. Venable, H. P.: J. Nat. M. A., 50:79, 1958.



DIAMOX®

HCO_3 regulating diuretic

Acetazolamide Lederle

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

NEW

AO Vistamatic

GIANTSCOPE

BRIGHTER: Now a higher than ever concentration of light, free from chromatic aberrations and shadows, controlled by a rheostat conveniently located right on the handle. No need to fumble with distant transformer controls. Special 6.5 volt bulb is precentered and prefocused... you can change bulbs in seconds. Intense illumination makes every examination easier and clearer, even when cloudy vitreous or ocular opacities hamper observations.

COOLER: Air space within double-walled handle limits heat transfer...keeps the instrument cooler even after long periods of constant use.

TRUE ONE-HAND OPERATION: All control dials are actuated with thumb or forefinger of hand holding instrument. A full selection of apertures, lenses and filters can be individually and quickly dialed into place.

AUTOMATIC LENS DIAL: Gives you an uninterrupted lens flow from +23.00D to −40.00D...in single dioptric steps. You make direct reading of lens power in viewing aperture. Dioptric scale is illuminated and magnified.

ELECTRA CASE: Smart-looking and compact...fitted with built-in transformer...just plug into any 110 volt outlet. Take your Giantscope with you wherever you go.

See this revolutionary intense illumination Giantscope in your own office. Mail handy coupon today.

American Optical
COMPANY

INSTRUMENT DIVISION, BUFFALO 15, NEW YORK

Dept. G253

☐ Please have my AO Sales Representative or Instrument Supplier demonstrate AO's New Vistamatic Giantscope.

☐ Please send complete literature on AO's New Vistamatic Giantscope.

Name_____

Address_____

City_____ Zone____ State_____

Information on a new Alcon product, reprinted from its accompanying explanatory leaflet

MYDRIACYL™

Brand of bis-Tropamide
for
CYCLOPLEGIA and MYDRIASIS

RAPID ACTING . . . MODERATE DURATION . . . RAPID RETURN

Mydriacyl, brand of bis-Tropamide, is a new compound pharmacologically related to the parasympatholytic (anticholinergic) group. The activity of this compound as a mydriatic-cycloplegic is extremely high and its solutions are virtually free of undesirable properties such as irritation and odor.

Its action is remarkable in that maximal mydriasis and cycloplegia are obtained within 20-25 minutes following instillation in the eye. Complete recovery occurs within 5-6 hours without the use of a miotic.

INDICATIONS FOR CYCLOPLEGIA: Mydriacyl is effective in those cases where cycloplegia is necessary. It has been demonstrated to be particularly effective in eyes having highly pigmented irides. One or two drops of Mydriacyl 1.0% has been demonstrated to produce a *maximal loss of accommodation within 20-25 minutes* which is not less than that obtained by other drugs commonly employed for this purpose. Its efficacy has been demonstrated in all age groups. The period of duration of maximal cycloplegia has been shown to be approximately 20 minutes followed by a rapid return to normal. Physiological recovery occurs within 2 to 4 hours with complete recovery occurring within 6 hours.

INDICATIONS FOR MYDRIASIS: Approximately equal mydriasis is produced by Mydriacyl 0.5% or Mydriacyl 1.0%. It has been demonstrated, however, that the degree of difference in cycloplegia between the two elects Mydriacyl 0.5% as the product of choice when mydriasis alone is the only factor desired. *Maximal mydriasis has been demonstrated to result from the instillation of one or two drops of Mydriacyl within 20-25 minutes.* This maximal persists for approximately 20 minutes followed by a rapid return to normal, usually within 3-4 hours without the aid of a miotic. Maximal mydriasis may be maintained by the instillation of drops every thirty minutes throughout the period desired. If necessary, the instillation of pilocarpine hydrochloride will bring about a more rapid return to normal.

CONTRAINDICATIONS: It has been demonstrated[1] that Mydriacyl has no tendency to increase intraocular pressure, and also that the compound has been used as a mydriatic in persons of extreme age[2]. In some cases[1,3] it was shown to actually effect a slight lowering of intraocular pressure, but in general there was no measurable effect. Due to the short duration of action, this danger usually associated with mydriatics is probably not great; however, caution should always be exercised in the instillation of any mydriatic in the eye, especially in those cases where the pressure is either unknown or has been found to be high.

CHEMISTRY: Mydriacyl, brand of bis-Tropamide, is a synthetic compound, Tropic acid-N-ethyl-N-(gamma-picolyl)amide. It has white, crystalline appearance, having a melting point of 96-96.5° and possesses a slight degree of solubility.

Mydriacyl is prepared as a boric acid solution containing phenylmercuric nitrate 1:50,000 as a preservative. The pH of the solution is approximately 6.2.

PHARMACOLOGY: The mydriatic effect of Mydriacyl was tested in the un-anesthetized eyes of albino rabbits and dogs.[4] The eyes were studied using the method of Draize *et al.*,[5] to determine if any injurious effect resulted. These tests demonstrated the extreme non-toxic and non-irritating effect of Mydriacyl. Studies demonstrating the effect on corneal tissue regeneration[4] showed Mydriacyl to exhibit no adverse effect.

A pharmacological investigation[4] was made of the general systemic effects of Mydriacyl on rabbit and dog hepatic, spleenic and renal tissues, as well as complete studies of the eyeball and accessory eyelid structures *en toto*.

As a result of this testing, it was shown that solutions of Mydriacyl in concentration as great as 5% produced no significant pathological alteration. Toxic effects were noted only at high levels. The Mouse LD_{50} is 277 mg./Kg. I.V. and 490 mg./Kg. I.P.

CLINICAL: The marked advantages of bis-Tropamide as a mydriatic-cycloplegic has been reported by several investigations.[1,2,3,6,7] Comparisons of the mydriatic-cycloplegic effect of Mydriacyl showed it to produce greater mydriasis than is produced by other drugs commonly employed for this purpose. In cycloplegia, it was found that equal or greater loss of accommodation resulted from Mydriacyl than resulted from other drugs, and that the return to normal was exceptionally rapid.

In both areas, the maximal was obtained within 20-25 minutes following instillation with a complete recovery occurring within 6 hours, more rapid in several cases.

Objective determination of irritation, itching, allergic or sensitivity reactions revealed the product to be void of these properties. Pretreatment prior to the time of examination was found to be unnecessary.

HOW SUPPLIED: Mydriacyl is supplied as a sterile ophthalmic solution of two strengths, (0.5% and 1.0%) in Alcon's plastic Drop-Tainer.

STORAGE: Stability studies on Mydriacyl reveal the formulation to be remarkably stable over a wide range of temperature and conditions. As with any medicinal product, however, prolonged storage in areas of high temperature should be avoided if possible.

REFERENCES:
1. Laboratory Report, Clinical Investigations of Mydriacyl as a Mydriatic-Cycloplegia, Alcon Laboratories, Inc. 2. Rintelen, F.: *Bull. schweiz. Akad. med. Wissensch. 13*:294, 1956. 3. Staenglen, K.: *Deutsche med. Wchnschr. 82*:481, 1957. 4. Laboratory Report, Laboratory Investigations of Mydriacyl, Alcon Laboratories, Inc. 5. Draize, J. H.; Woodward, G., and Calvern, H.: J. Pharmacol. & Exper. Therap. *82*:377, 1944. 6. Hollwich, F.: *Klin. Monatsbl. Augenh. 129*:685, 1956. 7. Vilmar, K. F., and Buchmann, H. H.: *Ophthalmologica 135*:114, 1958.

Mydriacyl is now available for your use from Pharmacies throughout the U.S.

Alcon ALCON LABORATORIES, INC., Fort Worth, Texas

a second prescription need

JOSEPH CORBETT, JR., also known as: James Barron, Joe Corbett, Walter Osborn, William Osborn, Charles Osborne, W. William Osborne, Walter Osborne, and others.

JOSEPH CORBETT, JR., is being sought by the FBI for Unlawful Flight to Avoid Confinement for the crime of murder.

On March 16, 1951, at Marin County, California, CORBETT was sentenced to a term of five years to life after entering a plea of guilty to a charge of second degree murder in the brutal gunshot slaying of an Air Force Sergeant. On August 1, 1955, he escaped from the California Institution for Men, Chino, California. A complaint was filed before a U.S. Commissioner at Los Angeles, California, on March 21, 1960, charging CORBETT with fleeing the State of California to avoid confinement for the crime of murder.

CORBETT has been convicted for murder and escaped confinement. He has been in possession of firearms since his escape. CORBETT should be considered armed and extremely dangerous.

DESCRIPTION:

Born:	October 25, 1928, Seattle, Washington
Height:	6'-6'2"
Weight:	160-170 lbs.
Build:	Medium
Hair:	Light brown
Eyes:	Hazel, wears glasses
Occupation:	Alkyd cooker (paint manufacturing), clerk-typist, laboratory technician, laborer, warehouseman
Scars and Marks:	Mole under chin, crescent-shaped scar right thumb, scar right side of abdomen.

REMARKS:

Allegedly left-handed and nearsighted; reported to be proficient typist and neat dresser.

Eyesight and Glasses

The last time CORBETT was known to have been fitted for glasses was on March 12, 1956. At that time his eyesight was as follows:

Right eye —400	
Left eye —200	
Pupillary distance (distance between pupils):	66MM
Eye size (width of lens at widest point):	46MM
Bridge of nose:	22MM

The type of lens used was a Cruxite A, which is slightly but not noticeably tinted.

The frame was a Manbow style, black Century frames, manufactured by the Universal Optical Company.

Any person having information which might assist in locating this fugitive is requested to notify immediately the Federal Bureau of Investigation, the telephone number of which may be found on the first page of local telephone directories.

AMERICAN JOURNAL OF OPHTHALMOLOGY

SERIES 3 · VOLUME 50 · NUMBER 1 · JULY, 1960

CONTENTS

(Table of Contents continued on page 212)

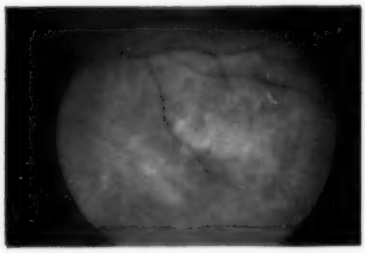


Fig. 2

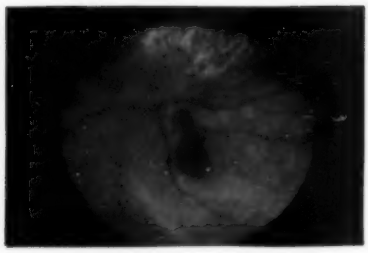


Fig. 3

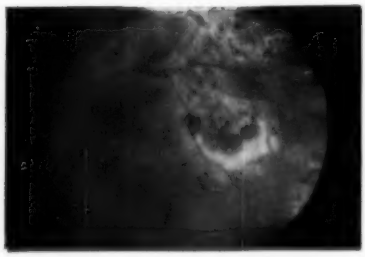


Fig. 4

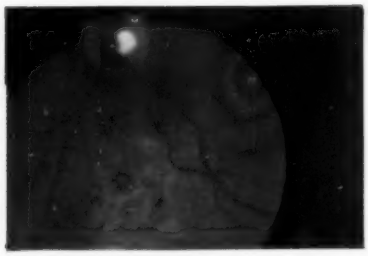


Fig. 13

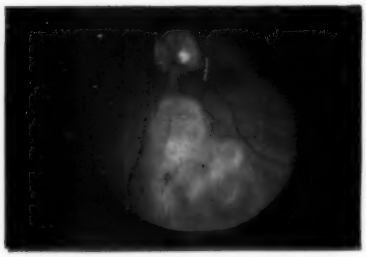


Fig. 14

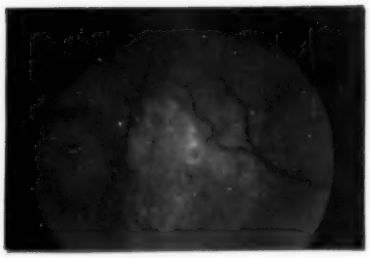


Fig. 15

Figs. 2, 3, 4, 13, 14, and 15 (MacLean and Maumenee). Hemangioma of the choroid.

Fig. 2. Case 2. Fundus photograph of the left eye, showing a pink-colored hemangioma of the choroid above the upper pole of the disc and macular area.

Fig. 3. Case 2. Fundus photograph of the left eye, showing results three months after treatment of the tumor by transscleral irradiation and penetrating diathermy.

Fig. 4. Case 2. Fundus photograph of the left eye, showing the appearance one year after treatment of the tumor by transscleral irradiation and penetrating diathermy.

Fig. 13. Case 7. Fundus photograph of the right eye, showing an orange-pink tumor (hemangioma) of the choroid in close proximity to the lower pole of the disc.

Fig. 14. Case 7. Photograph showing the result of photocoagulation six days after operation.

Fig. 15. Case 7. Photograph showing area of photocoagulation 23 days after operation.

AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 50 JULY, 1960 NUMBER 1

HEMANGIOMA OF THE CHOROID*

ANGUS L. MACLEAN, M.D., AND A. EDWARD MAUMENEE, M.D.
Baltimore, Maryland

Hemangioma of the choroid is a comparatively rare tumor, but one which probably occurs more often than reports in the literature would indicate. In about 50 percent of the cases reported, there has been a nevus flammeus on the ipsilateral side of the face. The choroidal tumor usually arises in the posterior portion of the fundus, frequently between the macula area and the disc. It is usually somewhat oval in shape. The area of choroidal involvement may be quite extensive, but in eyes with useful vision, the tumor mass has usually been limited to an area of six disc diameters or less. The color of the lesion has been variously described as grayish-blue, grayish-green or pink. Sector-shaped field defects, when present, have aided in the diagnosis. The rate of growth of the tumor is usually slow, but if unchecked, results in extensive retinal detachment from the accumulation of subretinal fluid. This is often followed by intractable secondary glaucoma.

The first recognized case of hemangioma of the choroid to be reported was that of Panas and Remey in 1879.[1] Leber had previously reported a case in 1869,[2] but had classified it as a spindle-cell sarcoma of cavernous structure. In recent years several excellent reviews of the literature have been published in conjunction with case reports.[3-5] No attempt has been made to check each case but it appears that more than 80 cases have been described. In the majority of instances, the diagnosis has been a retrospective one, being established only on histologic examination. The eyes have been removed because of suspected melanoma, or because they were blind and painful from extensive retinal detachment and intractable secondary glaucoma.

In spite of the fact that the diagnosis of hemangioma of the choroid has usually been made after enucleation, there have been excellent descriptions of the clinical appearance and the course of the lesion.[6-8]

There are two schools of thought as to the management of hemangioma of the choroid. One has suggested that the lesion is so rare and so closely resembles a melanoma, that unless nevus flammeus of the same side of the face is present, the eye should be enucleated. Others have advocated eradication of the tumor mass in an attempt to save the eye. The only instance in which the latter therapy has been successfully performed was in a case reported by Schepens and Schwartz.[5] This patient had a bilateral hemangioma of the choroid with extensive retinal detachments. In one eye the tumor was biopsied and histologic evidence of a hemangioma was obtained. All vision in this eye was eventually lost. In the remaining eye, the tumor was obliterated by trans-scleral diathermy and the patient regained 20/200 vision, and retained this for at least three years after the operation.

It is the purpose of this report to present the clinical picture and therapeutic outcome of eight cases of choroidal hemangioma. In

* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital. Presented at the 95th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May, 1959. The color plate accompanying this paper was sponsored by Jenkel-Davidson Company, San Francisco, California.

all but one of these cases (Case 3) a clinical examination was done by one of us. Most of the patients had been referred for consultation with a diagnosis of suspected melanoma. In only one instance was a small facial hemangioma present.

Case reports

Case 1

The patient, Stanford University Hospital No. 49-178 S.C.M., a white man, 40 years of age, is a policeman and had had yearly visual examinations. In November, 1948, his visual acuity was found to be 20/20 in each eye. On June 30, 1949, he noticed a blurring of vision in the right eye during pistol target practice.

He was seen in consultation in July, 1949, and at that time was found to have a corrected visual acuity of 20/50 in the right eye and 20/15 in the left eye. There was a pie-shaped visual field defect which began at the blindspot and extended upward temporally in the right eye. Just below the disc there was a lesion of approximately three or four disc diameters in size that was elevated eight diopters. The tumor was pink in color and transillumination of the mass was lighter than the remainder of the fundus. With the Friedenwald slit-ophthalmoscope, a reduplication of the beam could be seen. The macular area was detached but the periphery of the retina was flat. Provisional diagnosis were a nonpigmented melanoma, neurofibroma of the choroid, or hemangioma. The left eye was normal. Because of the possibility of a nonpigmented melanoma, enucleation was advised.

Histologic examination of the eye revealed a typical hemangioma of the choroid with cystic degeneration of the retina overlying the tumor mass in all layers, including the nerve fiber layer (fig.1).

Case 2

The patient, Stanford University Hospital No. E-1234719 J. G., a white man, truck driver, 30 years of age, was first seen in consultation on February 16, 1955. He stated that three years prior to that time he had noted spots and flashes of light in front of his left eye. He had seen an optometrist who prescribed glasses for him. Four weeks prior to his examination, visual acuity in his left eye had suddenly decreased.

On examination, the vision in the right eye could be corrected to 20/20 and in the left eye to 20/400. Refractive error RE —0.50 sph., LE emmetropic. Visual field examination revealed a sector-shaped defect in the nasal field.

The right eye was normal.

On ophthalmoscopic examination there was a honey-comb pink mass located just above the macula area that was three disc diameters wide and five to six disc diameters long, elevated two to three diopters (fig. 2). There was a slight accumulation of pigment along the margin of the tumor mass. The retina was slightly detached over the entire mass and the detachment extended down into the macula. There were a few striae in this area.

On examination with the slitlamp and contact lens, the retina appeared to be two to three times normal thickness and the lesion appeared more red and suggestive of blood vessels rather than a solid pigmented mass. *No specks of pigment were noted on the surface of the lesion.*

A cobalt blue filter was placed in front of the beam of the Haag-Streit slitlamp and the patient was given two cc. of 5.0-percent fluorescein intravenously. A dozen small spots in the central portion of the tumor fluoresced within 30 seconds.

A diagnosis of hemangioma of the choroid was made.

On March 10, 1955, the tumor was coagulated with a 1.5 and 2.0 mm. electrode by means of transscleral

Fig. 1 (MacLean and Maumenee). *Case 1.* Microscopic section of the posterior segment of the right eye, showing a typical cavernous hemangioma of the choroid in close proximity to the disc and slight separation of the retina.

diathermy. Following this two radon seeds each containing 2.5 mc. of radon were sutured to the sclera over the tumor mass. It was estimated that 3,000 roentgen equivalents would be applied to the tumor three mm. from these seeds.

Immediately following operation some hemorrhage was noted in the deeper part of the tissue and the patient's visual acuity fell to counting fingers at two feet. By May 24, 1955, the diathermy reaction had begun to subside and the visual acuity improved to 20/300 (fig. 3). By August, 1956, the visual acuity had improved to 20/30 and has remained at that level until the time of publication of this report (fig. 4).

CASE 3

This patient, Stanford University Eye Pathology No. 54-77, F. K., a white woman, 34 years of age,* was not examined clinically by either of us, but the histologic specimen was examined by one of us. The history is so typical that it is being included in this report.

The patient was first seen in 1950 for routine examination. At that time she gave a history of lowered visual acuity for an indefinite period in the left eye. Her corrected vision in the right eye was 20/20 and in the left eye 20/60. The patient's vision continued to fail and in February she was seen by Dr. Arthur Kahler. At that time her visual acuity in the left eye was limited to hand motions. There was an extensive bullous detachment of the entire inferior retina. In the macula region there was a solid mass which measured four disc diameters horizontally and three vertically and was elevated three to four diopters. The lesion had a pink tinge as compared to the surrounding retina. On examination with the slitlamp it appeared solid and contained a large number of blood vessels. *There was no evidence of pigment on the suface of the mass.*

The right eye was normal.

The left eye was enucleated because of a suspected melanoma. On histologic examination there was a typical hemangioma of the choroid in the macula area. The inferior retina was detached by a serous coagulum. The retina overlying the tumor showed extensive cystic degeneration of all layers including the nerve-fiber layer. The pigment epithelium over the tumor was thin, distorted, and some of it was missing. There was no evidence of new-formed fibrous tissue between the retina and choroid.

CASE 4

Johns Hopkins Hospital No. 660717. V. B., a white man, civil service employee, 36 years of age. Vision of the right eye had been blurred for several months, and there was a relative central scotoma for colors and a sector defect in the lower field extending from close to the point of fixation completely to the periphery (fig. 5). The first examination disclosed an oblong lesion in the upper part of the area between the macula and the disc. By

* This case is presented by the kind permission of Dr. Arthur Kahler, Sacramento, California.

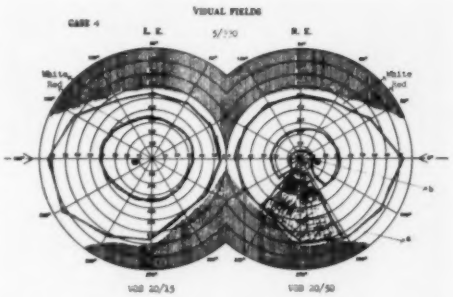


Fig. 5 (MacLean and Maumenee). *Case 4.* Visual fields, showing the characteristic sector-shaped defect in the right eye. Areas of absolute blindness mixed with areas of relative blindness (a), and a relative central scotoma (b).

direct illumination this lesion had a greenish-yellow spongy appearance, but on retroillumination it appeared streaked or honeycombed with darker lines in the lighter background. There was no obstruction to light on transillumination. It was generally agreed that this was not an inflammatory lesion. The eye was not enucleated, and the patient was kept under observation.

The left eye was normal.

In the course of a year the lesion (fig. 6) increased in size, became more elevated, and the color changed to a uniform grayish-pink or orange-pink. There was some separation of the retina, particularly at the lower dependent portion, giving the appearance of an overhanging lower border above the macula and the disc.

In September, 1955, a diagnosis of hemangioma of the choroid was made. The tumor was coagulated by transscleral diathermy, and a one-half millicurie radon seed was sutured to the episclera in this area. Figure 7 is a photograph of this fundus six months later. It shows not only the scars from the coagula-

Fig. 6 (MacLean and Maumenee). *Case 4.* A large and elevated orange-pink tumor, above and temporal to the disc, with slight separation of the retina at the lower dependent portion. (September, 1955.)

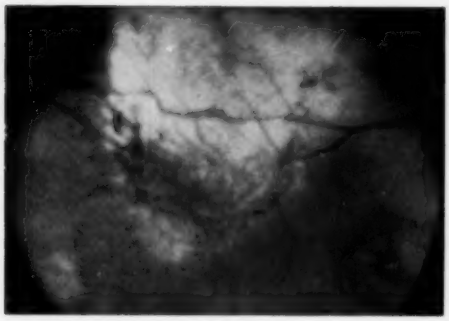


Fig. 7 (MacLean and Maumenee). *Case 4.* Fundus photograph, showing results six months after treatment of the tumor by transscleral irradiation and penetrating diathermy. A large area of scarring is seen at the upper and temporal side.

tion, but also evidence of a residual tumor. Diathermy treatment was repeated one year later. This was also unsuccessful. In six months' time the extension had reached beyond the disc to the nasal side.

The patient was seen by Prof. Meyer-Schwickerath who concurred in the diagnosis. Although there was some subretinal fluid, he believed that the degree of retinal separation was still within the limits of safety and that light coagulation could be given. Since the macula was already involved, treatment was given only with the idea of saving the eye. Accordingly, sparing the macula as much as possible, the entire growth was given about 25 exposures of light coagulation of moderate intensity. This treatment was followed by marked ischemic reaction which lasted for a few weeks (fig. 8). In the course of the next five months, the entire growth was replaced by scar tissue (fig. 9). The cure has been complete as far as eradication of the tumor is concerned. Unfortunately, the successful therapy was instituted too late to save useful vision.

Fig. 8 (MacLean and Maumenee). *Case 4.* Fundus photograph, showing the ischemic reaction one week following treatment of the tumor by light coagulation.

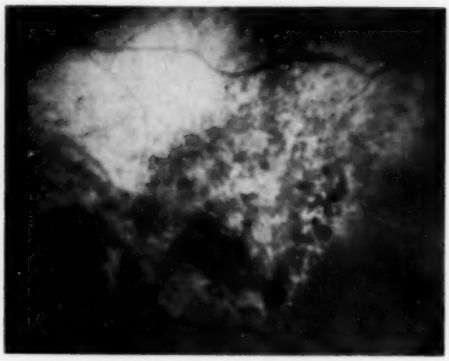


Fig. 9 (MacLean and Maumenee). *Case 4.* Fundus photograph, showing the appearance seven months after treatment of the tumor by light coagulation. The entire area of the tumor is replaced by scar tissue.

CASE 5

The patient, J. N. McD., Capt., U.S.N., a white man, 43 years of age, had first noticed blurring of vision in April of 1955. At that time, his corrected visual acuity in the right eye was 20/50 and in the left eye 20/20. A mass was noted inferior to the macula. It was approximately two disc diameters in size and elevated three to four diopters. There was a superior nasal field defect that reached to within 15 degrees of the point of fixation (fig. 10).

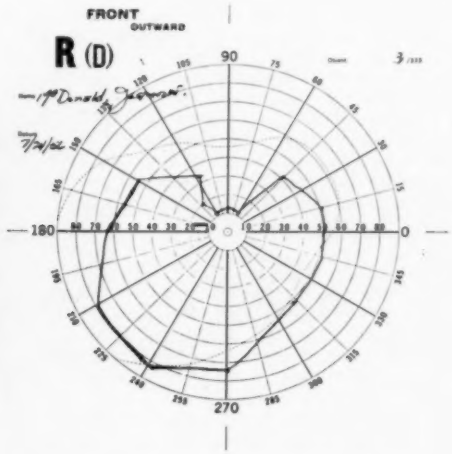


Fig. 10 (MacLean and Maumenee). *Case 5.* Visual-field defect.

In August, 1955, his visual acuity was recorded as 20/30-2. Cycloplegic refraction was +0.25D. sph. ⊂ −0.50 D. cyl. ax. 45° in the right eye and +0.25D. sph. ⊂ −0.25D. cyl. ax. 120° in the left eye. This was essentially what the patient had been wearing.

He was seen in consultation in July, 1956, and a diagnosis of hemangioma of the choroid of the right eye was made. This was based on the pink appearance of the tumor mass, *the lack of pigment over the tumor on slitlamp examination*, the lack of growth of the lesion over a period of one year, and the sector-shaped field defect.

The left eye was normal.

A blood pressure cuff was placed around the patient's neck and inflated to 35 to 40 mm. Hg. The intraocular pressure in the two eyes became elevated to exactly the same degree.

The patient was discharged from the Navy and has not been seen by us since April, 1957.

CASE 6

This nine-year-old white girl, Johns Hopkins Hospital Harriet Lane History No. 17113, D. W.,* was examined in the spring of 1957 because she had some difficulty with her school work. No abnormality of her eyes was found except for slight hyperopia of the right eye. In December, 1957, the right eye turned outward. Examination at this time revealed a tumor in the right fundus.

The patient was seen in consultation by Dr. Frank Walsh on January 16, 1958. Visual acuity in the right eye was 5/200 with eccentric fixation, and 20/20 in the left eye. Visual field examination revealed a loss of all but the temporal half of the field to a 15/330 white test object. The right eye deviated externally 15 prism diopters.

On ophthalmoscopic examination of the right eye, a large, gray, round tumor mass 10 to 15 times the size of the disc, elevated eight diopters, was noted temporal to the macula area. There was an absence of pigment in and on the tumor except at the temporal margin of the lesion. The retina was detached over the tumor and to the periphery of the fundus. The detachment extended from the 6-o'clock to the 10-o'clock meridians. No hemorrhage was noted about the lesion. One observer noted that the color of the lesion suggested a hemangioma.

The left eye was entirely normal.

Since the right eye was almost blind and a definite tumor mass could be seen, it was decided that enucleation was the safest procedure. Microscopic examination of the eye revealed a typical cavernous hemangioma of the choroid, with extensive retinal detachment and cystic degeneration of the retina overlying the tumor (fig. 11).

CASE 7

The patient, Johns Hopkins Hospital History No. 828787, J. H., a white woman, 36 years of age, first noted some flickering of light and blurring of vision in her left eye in July, 1958. In October, 1958, she was found to have a solid tumor just inferior to the disc and a serous detachment of the retina inferiorly. She was referred for consultation because of a suspected melanoma of the choroid.

This patient was first seen in consultation on November 14, 1958. At that time her corrected visual acuity in the right eye was 20/15 and in the left eye 20/20. Her refractive error in the right eye was −0.75D. sph. ⊂ −0.25D. cyl. ax. 90° and in the left eye −0.75D. cyl. ax. 30°. A visual field examination revealed a superior loss of field down to the point of fixation in the left eye (fig. 12).

The right eye was normal.

On ophthalmoscopy of the left eye, there was a honey-combed pink mass (lighter color than the re-

* This case is presented by the kind permission of Dr. Frank Walsh of Baltimore, Maryland.

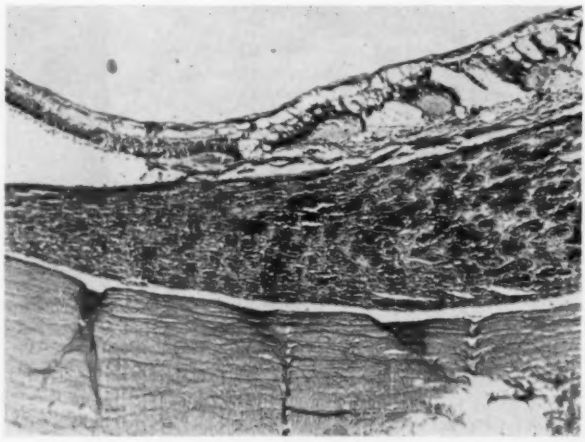


Fig. 11 (MacLean and Maumenee). *Case 6.* Microscopic section of the posterior segment of the right eye, showing a typical cavernous hemangioma of the choroid with the retina attached at the upper border but detached, with high elevation, from that point to the ora below. Also showing cystoid degeneration of the retina.

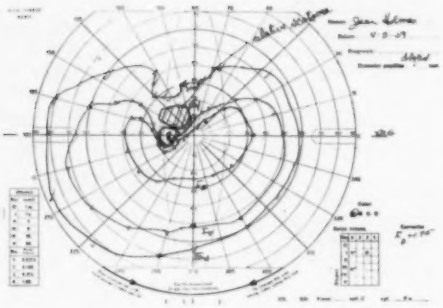


Fig. 12 (MacLean and Maumenee). *Case 7.* Visual-field defect.

mainder of the fundus) lying just below the disc and somewhat oval in shape. It was approximately four disc diameters wide and five to six diameters long and was located primarily between the nasal and temporal branches of the inferior retinal artery (fig. 13). There was a serous detachment of the retina which shifted readily from the ora serrata when the patient was sitting up to the inferior margin of the tumor mass when the patient was lying on her back. The detachment covered ap proximately one third of the inferior retina and was elevated about eight diopters when the patient was lying flat. The retina overlying the tumor was not detached.

Examination with the slitlamp and contact lens revealed that the lesion was more red in color than the surrounding fundus and appeared to contain a number of blood vessels. *There was no pigment on the surface of the lesion* or surrounding the margin of the mass. The patient was observed with a cobalt blue lens placed in front of the Schepens binocular ophthalmoscope and 10 cc. of five percent fluorescein was injected intravenously during a period of about two minutes. When approximately five cc. of fluorescein had been injected, the tumor mass fluoresced beautifully.

A blood pressure cuff was placed around the patient's neck and inflated to 35 to 40 mm. Hg. The intraocular pressure in the two eyes became elevated equally.

A diagnosis of hemangioma of the choroid with secondary detachment of the retina was made. The patient was followed on frequent examinations until June 15, 1959. There was no change in the visual field defect or the size of the tumor during this time.

On June 15, 1959, the lesion was coagulated with about 15 to 20 applications of the Meyer-Schwickerath light coagulator. An effort was made not to occlude the major branches of the nasal and temporal artery and veins. Following photocoagulation, the treated area became entirely white (fig. 14). By June 29, 1959, some pigmentation in the area of the lesion could be observed. The retinal detachment, at that time, had not changed. On July 8, 1959, further pigmentation of the mass could be observed (fig. 15), and the retinal detachment had disappeared completely. The patient's visual acuity at that time was 20/25, corrected.

CASE 8

This patient, M. J. V., a white soldier, 23 years of age, had had a nevus of his left eyelid and forehead since birth (fig. 16). He stated that the visual acuity in his left eye had been progressively failing for the past two years.

On examination he was found to have a normal right eye with normal visual acuity. The visual acuity in his left eye was reduced to light perception. On ophthalmoscopic examination, the patient was noted to have an extensive retinal detachment covering the entire inferior half of his fundus. This detachment extended out to the ora serrata. Immediately above the disc, there was an orange-pink tumor that measured about six disc diameters in size and was elevated three diopters. There was a ring of increased pigmentation around the margin of the mass. Slitlamp examination of the fundus *failed to show any evidence of pigment flecks over the surface of the tumor.*

The subretinal fluid shifted very easily in this patient, so that when he was lying flat on his back the posterior pole of the retina was detached, including the retina overlying the tumor. When he was sitting up, however, the entire subretinal fluid drifted to the inferior portion of his fundus.

It was thought that it might be possible to save some visual acuity for this patient if his retina could be reattached and the tumor obliterated. It was also thought that if the tumor could be obliterated and the patient did not regain better vision, that this would possibly prevent the eye from deteriorating further. For this reason an attempt was made to drain the subretinal fluid at the 6-o'clock position. This was not successful, possibly because the subretinal fluid drifted to the posterior portion of the fundus when he was lying

Fig. 16 (MacLean and Maumenee). *Case 8.* Photograph showing nevus flammeus on the ipsilateral side of the face.

on his back. Approximately three days after the attempt had been made to drain the subretinal fluid, photocoagulation was applied to the tumor mass. Approximately 10 applications of light were applied to the tumor. It was felt that more extensive coagulation should not be done because of the presence of the retinal detachment. Over a period of the next three months, only very slight pigmentation occurred in the area of light coagulation.

It was thought that before further light coagulation should be applied to the tumor that another attempt should be made to reattach the patient's retina. This was done and the reattachment operation was not successful. Following operation, the patient's visual acuity was no light perception. The fundus, however, remained approximately the same in appearance. The inferior portion of the retina was highly detached, and an area of puckering in the retina could be seen inferiorly where the fluid had been drained. The tumor mass above the disc was approximately the same as it had been prior to therapy. Because the patient's visual acuity was reduced to no light perception, it was felt that further operative procedures were contraindicated.

Comment

In these eight patients, the sex incidence was divided almost equally between male and female. All were of the white race. A few spider hemangiomas of the skin were present in one patient but only one showed a nevus flammeus on the ipsilateral side of the face.

In three of the patients in this series the diagnosis was confirmed by microscopic examination of the enucleated eye. In five patients the diagnosis was made purely on a clinical basis. One of these five patients was treated and cured by transscleral diathermy plus irradiation (Case 2). One was treated by diathermy and irradiation but the complete tumor was not obliterated. Subsequently the remainder of the tumor was destroyed by photocoagulation (Case 4). The tumor in Case 7 was obliterated by photocoagulation but the lesion in Case 8 was not completely occluded by this technique.

In each of the three eyes enucleated, the tumor was a typical cavernous hemangioma and the histologic structure in each was strikingly similar. Each was fusiform in shape and blended in with the surrounding choroid. There were innumerable thin-walled vascular spaces, which in some areas appeared to be lined by a single row of endothelial cells. In other areas the stroma between the cavernous spaces was thicker. These spaces contained blood. The retina overlying the tumor showed extensive cystic degeneration of all layers. The involvement of the nerve fiber layer probably accounts for the sector-shaped visual field defect.

Diagnostic signs

1. *Location.* The tumor mass is usually located in the posterior part of the fundus close to the optic disc. Not infrequently it is in the macula area. The most helpful feature in making a diagnosis of this tumor is its color. The lesion is usually lighter in color than the remainder of the fundus and at times appears to be honeycombed because of very faint white connective tissue which overlies the tumor mass (see photographs of Cases 2 and 7). The light color of the tumor is due to the lack of pigmentation both in the tumor and on its surface. This can be most clearly seen when the lesion is examined with the slitlamp and contact lens. No flecks of pigment are observed on the surface of the tumor. This is in contrast to melanomas where considerable pigment can be seen with this technique. Even in amelanotic melanomas a few clumps of pigment can be seen on careful examination. At times there may be an increased pigmentation at the margin of the hemangioma, but this was observed in only two cases in our series. The lesion is usually relatively small and fusiform or oval in shape. All of the tumors except one (Case 6) in this series of patients were relatively small, that is, they measured not more than four to six disc diameters in their largest axes. Hemorrhages, which may rarely be present around small melanomas and which are almost always present around a disciform degeneration, were not found around these tumors. On retroillumination of the tumor with the ophthalmoscope light, the tumor appeared to be lighter than the remainder of the fundus.

2. *Visual fields.* The sector-shaped visual-

TABLE 1

SUMMARY OF EIGHT CASES OF HEMANGIOMA OF THE CHOROID

Case	Race and Sex	Age (yr.)	Diagnosis		General	Extensive Detachment	Color of Tumor	Sector Field Defect	Diathermy	Treatment		Result
			Microscopic	Clinical						Radon Seed	Light Coagulation	
(a) 1	W M	40	+	?	Neg.		Grayish-pink	+				Enucleated
(b) 2	W M	30		+	Neg.		Honeycombed Grayish-pink	+	+	+		Cured
(c) 3	W F	34	+		Neg.	+	Pinkish tinge	Large defect				Enucleated
(d) 4	W M	36		+	Neg.		Greenish-yellow to grayish-pink	+	++	+	+	Cured
(e) 5	W M	43		+	Neg.		Pinkish	+				
(f) 6	W F	9	+		Spider hemangioma	+	Dark gray mass	Large defect				Enucleated
(g) 7	W F	36		+	Neg.		Honeycombed pinkish	+			+	Cured
(h) 8	W M	23		+	Nevus flammeus ipsilateral	+	Orange-pink	Large defect			+	

Penetrating diathermy repeated once in Case 4.

field defect is not always present in hemangiomas of the choroid but, when it is, it is a helpful diagnostic sign in differentiating this lesion from a melanoma. The defect is probably caused by a cystic degeneration of the nerve fiber layer of the retina overlying the tumor. The field defect is particularly striking because of the small size of the lesion. A melanoma of this size would cause only a scotoma corresponding to the tumor (fig. 17).

3. *Transillumination.* Transillumination by the transscleral scatter technique reveals that the mass is lighter in color than the remaining area of the fundus.

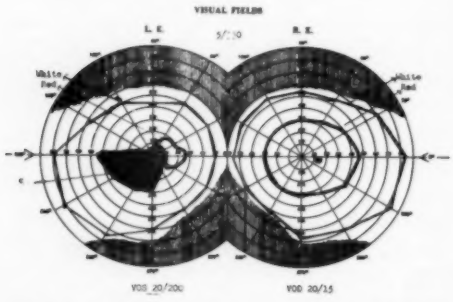


Fig. 17 (MacLean and Maumenee). Visual fields in a proved malignant melanoma of the choroid of the left eye, showing the characteristic absolute island scotoma.

4. *Retinal detachment.* Retinal detachments are frequent occurrences in hemangiomas of the choroid, and were present in five of the eight cases reported. The detachments are particularly striking because of the small size of the tumor. Melanomas of this size seldom produce retinal detachments.

5. *The fluorescein test.* A fluorescein test was devised to study these cases with the hope that it might aid in differentiating these tumors from melanomas. The technique is as follows: A light is prepared by placing a cobalt blue filter (Haag-Streit) either in front of the Haag-Streit slitlamp or in front of the light of the Schepens binocular ophthalmoscope. The patient's pupil is widely dilated. The examiner stays in a dark room for about five minutes to allow his eyes to adjust to the light. Ten cc. of five-percent fluorescein* is then injected intravenously over a period of about two minutes by an assistant. When approximately five cc. of fluorescein has been injected, the retinal vessels become greenish-yellow in color, the arteries filling first and the veins filling thereafter. Almost immediately after this, the blood spaces in

* Made by C. F. Kirk Co., 521 West 23rd Street, New York, New York.

the cavernous hemangioma fluoresce.

Unfortunately, this test is not specific for hemangiomas of the choroid because other lesions such as amelanotic melanomas, disciform degeneration of the macula, and other chorioretinal lesions where the choroidal vessels are exposed, also fluoresce with this technique. It should be pointed out, however, that heavily pigmented melanomas show very little evidence of fluorescence; therefore, if a lesion does not fluoresce, hemangioma of the choroid may be excluded.

6. *X-ray studies.* Osseous and calcareous changes have occasionally been noted on microscopic examination between a hemangioma of the choroid and retina. Therefore, X-ray studies of the eye may be of value in diagnosing a long-standing hemangioma of the choroid, but will probably be of no value in early lesions. In the cases described in this report, none of the eyes showed calcification of the choroid on histologic examination.

Conclusions

1. Hemangiomas of the choroid can be diagnosed clinically and differentiated from melanomas.

2. Hemangiomas of the choroid can be obliterated by transscleral diathermy, application of randon seeds and photocoagulation. Photocoagulation of the tumor is the easiest method of treatment.

The Johns Hopkins Hospital (5).

References

1. Panas, F., and Ramey, A.: Anatomie pathologique de l'oeil. Paris, 1879.
2. Leber, T.,: Case of cavernous sarcoma of the choroid. Arch. f. Ophth., **14**:221, 1868.
3. Rosen, E.: Hemangioma of the choroid. Ophthalmologica, **120**:127, 1950.
4. Danis, P.: Angioma of the choroid. Arch. ophtal., **12**:487, 1952.
5. Schepens, C. L., and Schwartz, A.: Intraocular tumors: I. Bilateral hemangioma of the choroid. A.M.A. Arch. Ophth., **60**:72, 1958.
6. Fehr, I.: Angioma of the choroid. Centralbl. Augenh., **29**:161, 1905.
7. Reis, W.: Clinical diagnosis of angioma of the choroid, Ztschr. Augenh., **26**:308, 1911.
8. Kreibig, W.: The clinical diagnosis of choroidal angiomas. Klin. Monatsbl. f. Augenh., **107**:597, 1941.
9. Von Hippel, E.: Angioma of the choroid. Arch. f. Ophth., **127**:46, 1931.
10. Meyer-Schwickerath, G.: Experiences with light coagulation of the retina and the iris. Documenta Ophth., **10**:91, 1956.

CORRECTION OF UNILATERAL APHAKIA WITH CONTACT LENSES*

Report of seven cases

John A. Dyer, M.D., and Kenneth N. Ogle, Ph.D.
Rochester, Minnesota

In a recent paper[1] it was pointed out that even though the aphakic eye is corrected with a contact lens in a patient with unilateral aphakia, theoretically, there remains a residual aniseikonia of about eight percent, the exact amount depending on the nature of ametropia of the eye prior to surgical intervention. For example, when the aphakic eye was corrected by a contact lens, the magnification of the retinal image of this eye compared to that of the emmetropic eye was greater if the eye was originally axially myopic than if it was axially hypermetropic.

Numerous reports are to be found in the literature to the effect that many patients do wear unilateral contact lenses comfortably in spite of the residual aniseikonia to be ex-

* From the Section of Ophthalmology and the Section of Biophysics, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

pected and, in addition, the aphakic patient seems to tolerate the contact lens more readily. It is not necessary to review the many reports to be found in the literature that stress the re-establishment of "normal" binocular vision by patients whose unilateral aphakia is corrected by contact lenses. It is sufficient to point out again that it is difficult to assess the value of these reports, especially with respect to the residual aniseikonic error to be expected. Most reports gave successful results only on the basis of subjective response of the patient during rather brief periods. Few tests for functional binocular vision have been made.

Numerous possibilities might help to explain these results. In the first place, the subjective tolerance may be due in part to an actual decreased corneal sensitivity to a foreign body in the eye, but associated with this factor is the role played by motivation of the patient that prompts him to ignore so-called minor irritations. On the physiologic side, however, there would be (1) a continued or developed suppression of binocular vision, especially in the peripheral parts of the field, (2) a lowered visual acuity in one eye, which permits less exact fusion of the images of contours, and (3) the suppression of stereopsis. These three aspects may be part of the hypothesis emphasized by Linksz[2] in that small aniseikonic errors may indeed be a source of ocular discomfort, whereas large differences may impair binocular vision to the extent that the patient loses the capacity of normal binocular co-operation.

Report of cases

In the seven cases to be reported the ages of the patients with unilateral aphakia corrected by nonscleral (corneal) contact lenses varied from 15 to 67 years. Follow-up tests were made from a few months to more than a year after correction of aphakia with contact lenses. In each case careful measurements were made by means of the space-eikonometer, and, where feasible, other more extensive tests for stereoscopic spatial localization also were made. All patients showed residual differences in the magnification of the images in the two eyes of 5.5 to 9.0 percent. The results will be discussed with respect to the patient's subjective ocular comfort, the time of fitting of the contact lens after operation, the resultant visual acuity, the wearing time, the continued use of the lenses, and finally the patient's stereoscopic spatial localization and binocular co-ordination in general.

Pertinent data concerning each patient are tabulated in Table 1 and include age, spectacle prescription for both the phakic and aphakic eyes, visual acuity with spectacle lens for each eye, visual acuity with contact lens on the aphakic eye, and the results from space-eikonometer measurements.

Case 1

A 15-year-old farm boy had a traumatic cataract successfully needled six months after injury to the right eye. The refractive error was +10.5D. sph. ⌒ −1.25D. cyl. ax. 160° for the aphakic eye and −1.5D. sph. for the phakic left eye; the visual acuity was 20/20 for each eye. A corneal contact lens was fitted to the right eye one month after operation, and again a visual acuity of 20/20 was obtained.

After five months, during which time the lens could be worn comfortably for 12 or more hours daily, the patient was re-examined. Visual acuity was still 20/20 with the contact lens worn on the right eye. The troposcope showed fusion at a convergence (eso) of 5Δ, and when medium second-grade slides were used the patient maintained fusion from 5Δ (base-in) to 20Δ (base-out). He could recognize stereopsis with the slides having large black and white details but suppressed the image of the right eye when the slides having fine details were used. Thus tests on the space-eikonometer could not be made.

The results of the examination made on the direct comparison eikonometer while the patient wore both the contact lens on the right eye and spectacles (plano before the right eye and −1.5D. sph. before the left eye) showed that the image of the left eye had to be increased eight percent (± 1.0 percent) to equalize the images. No stereopsis could be demonstrated on a horopter instrument,[8] for the patient failed to respond to different afocal meridional magnifying lenses placed before either eye.

This patient could wear a contact lens comfortably although he must have had near normal corneal sensitivity since only a needling operation had been performed. He

TABLE 1

PERTINENT DATA ON SEVEN PATIENTS WITH UNILATERAL APHAKIA CORRECTED WITH CORNEAL CONTACT LENSES

Case Number	Age of Patient (yr.)	Eye	Spectacle Prescription	Visual Acuity		Space-Eikonometer Findings	
				With Spectacle Lens	With Contact Lens	Axis	Difference in Magnification (percent)
1	15	Right	+10.5D. sph.⊂−1.25D. cyl. ax. 160°	20/20−	20/20−		L, 8.0±1.0 using direct comparison eikonometer target; no stereopsis
		Left	−1.5D. sph.	20/20			
2	16	Right	+9.75D. sph.⊂−1.0D. cyl. ax. 10°	20/20	20/20	90	L, 8.0±0.75
		Left	Plano	20/20		180	L, 7¾±0.75
3	47	Right	+1.0D. sph.⊂−1.0D. cyl. ax. 102°	20/30+		90	R, 7.0±1.0
		Left	+11.75D. sph.⊂−1.75D. cyl. ax. 90°	20/20	20/20	180	R, 7.5±1.5
4	16	Right	+11.75D. sph.⊂−1.0D. cyl. ax. 130°	20/30	20/30	90	L, 6.0±1.0
		Left	Plano	20/40+		180	L, 6.0±2.0
5	48	Right	+11.5D. sph.⊂−2.05D. cyl. ax. 92°	20/30+	20/30+	90	L, 9.0±1.25
		Left	+0.25D. sph.⊂−1.75D. cyl. ax. 88°	20/20−		180	L, 7.0±1.5
6	55	Right	+11.0D. sph.⊂−3.25D. cyl. ax. 95°	20/20−	20/20−	90	L, 7.5±0.75
		Left	Plano	20/30−		180	L, 8.0±1.0
7	67	Right	+3.12D. sph.⊂−0.62D. cyl. ax. 90°	20/25		90	R, 6.0±0.5
		Left	?	20/20	20/20	180	R, 5.5±0.75

L = left eye; R = right eye.

did not experience any symptoms of discomfort relative to use of his eyes or any unusual spatial distortions, in spite of eight-percent difference in magnification of images by the two eyes. Since the acuity of the eyes was also equal, what factor made this tolerance possible? The only objective suggestion comes from the reduced sensitivity to stereoscopic vision, for there was evidence of a constant tendency to suppress the image of the right eye in all tests requiring fine discrimination. Subsequent letters from the patient after he had used his contact lens for several months stated that he continued to wear the lens with comfort.

CASE 2

Another farm boy, 16 years of age, had had a single needling operation on the right eye for a traumatic cataract caused by a contusion two years prior to the operation. He had never worn glasses and his visual acuity was found to be 20/20 for each eye when a trial case lens of +9.75D. sph. ⊂ −1.0D. cyl. ax. 10° was placed before the right eye and a plano lens was placed before the left eye. A corneal contact lens was fitted to the aphakic eye one month after operation, with resultant visual acuity of 20/20. Examination of the patient one month later showed that he could wear the lens comfortably for 12 to 14 hours a day, during which time he did not experience diplopia, eye fatigue, or any ocular symptoms. Space-eikonometer measurements at that time were as follows: axis 90° : L, 6.5 ±0.5 percent; axis 180° : L, 6.5 ±0.5 percent.

The patient was re-examined 14 months later. It was found that most of the time he had not worn the lens because of the dust and so forth involved in farming. Although, according to his report, the lens could be tolerated well for several hours and he had no visual complaints, he stated that his vision seemed to be about the same whether or not he wore the contact lens. At this time the space-eikonometer measurements were: axis 90°: L, 8.0 ±0.75 percent; axis 180°: L, 7.75 ±0.75 percent. On the horopter instrument at an observation distance of 40 cm., he adjusted the positions of the wires for an apparent frontoparallel plane with roving fixation. First, no lens except the contact lens was used before the right eye; later a +1.5D. sph. was used in addition

to the contact lens. The curves defined by the positions of the wires were found rotated through a large angle, which showed that the image in the right eye was too large. On the small tilting apparatus[4] the patient apparently used some monocular judgment, since no effect was noted when an afocal lens was placed before either eye.

This young patient also tolerated a contact lens on a unilaterally aphakic eye for many hours, in spite of normal corneal sensation and normal visual acuity in both eyes and in spite of a difference in magnification between the images of the two eyes of seven to eight percent. One may assume that part of his tolerance to this lens was due to an imperfect stereoscopic function or, more pertinently, to his reliance on monocular spatial localization.

CASE 3

The visual acuity in the left eye of a 47-year-old physician had been reduced to light projection by a cataract. The right eye showed minimal incipient opacities of the lens with a visual acuity of 20/30+ when corrected by a spectacle lens of +1.0D. sph. ⊂ −1.0D. cyl. ax. 102°. Because the cataractous eye was an annoyance in his work, a linear extraction of the cataract was performed, and 10 months later a corneal contact lens was prescribed for the left eye. At that time the refractive error of the left eye was +11.75D. sph. ⊂ −1.75D. cyl. ax. 90° and correction by the contact lens resulted in 20/20 visual acuity.

Examination after two months revealed that he had worn the contact lens comfortably for 12 to 14 hours daily. The plano spectacle correction was used in addition to the contact lens for the left eye, a regular correction for the right eye, and a bifocal segment in both lenses for reading. Prior to extraction of the cataract the patient had not had binocular function for nearly two years.

The results of the space-eikonometer measurements were: axis 90°: R, 7.0 ±1.0 percent; axis 180°: R, 7.5 ±1.5 percent. With the Worth four-dot test he saw only four dots for both distant and near. The phorias as measured with the Maddox rod were 4Δ exophoria at far, and 8Δ exophoria at 40 cm. He had no visual complaints at this time nor did he have any up to a year later; he insisted his eyes functioned normally.

This patient also apparently tolerated an abnormal difference in magnification of the images in the two eyes. If it were necessary to find a reason for this, one would suspect that the reduced visual acuity in the unoperated eye contributed substantially to his visual comfort, which would in part minimize any undesirable effects.

CASE 4

A 16-year-old girl had reduced visual acuity of 20/200 for the right eye and 20/40 for the left eye as a result of congenital cataracts. Visual acuity was unimproved by lenses. First a linear extraction was performed and two years later a needling operation was performed on the right eye only. The refractive error of the right eye then was +11.75D. sph. ⊂ −1.0D. cyl. ax. 130°, and when corrected by a spectacle lens gave a visual acuity of 20/30. A contact lens was obtained for this eye, and two months later the patient was wearing this lens 10 hours daily apparently with comfort and binocular vision.

The results of the space-eikonometer measurements were: axis 90°: L, 6.0 ±1.0 percent; axis 180°: L, 6.0 ±2.0 percent. The reduced acuity of the other eye resulted in reduced sensitivity to the eikonometer test and also to other tests for binocularity.

In this case it is apparent that the lower visual acuity of one eye is the important factor that permitted the patient to tolerate the difference in the magnification of the images in the two eyes.

CASE 5

A 48-year-old woman had a complicated cataract of the right eye with vision decreased to that of counting fingers, though she showed good light projection. The visual acuity of the left eye was 20/20 with correction (+0.25D. sph. ⊂ −1.75D. cyl. ax. 88°). An extracapsular extraction was performed on the right eye, and four months later the refractive error was +11.5D. sph. ⊂ −2.75D. cyl. ax. 92°, which, when corrected, gave a visual acuity of 20/25+. The refractive error and corrected visual acuity of the left eye were the same as before.

Six weeks after obtaining a contact lens the patient was re-examined. She stated that she tolerated the lens well for about eight hours daily. With the contact lens her visual acuity was 20/30. The lens was difficult to fit properly, however, because of slight corneal irregularity. Measurements made while she wore the contact lens on the right eye and the spectacle prescription for the left eye showed exotropia of 20Δ for distant and for near vision with the cover test. With the troposcope, the objective angle was found at a divergence of 15Δ. Fusion was maintained with targets having peripheral details of two degrees, with a prism vergence of 12Δ (base-in) to 30Δ (base-out) (with medium second-grade targets to 22Δ base-out). She recognized stereopsis with difficulty with the slide targets having small details. The results of the space-eikonometer measurements were: axis 90°: L, 9.0 ±1.25 percent; axis 180°: L, 7.0 ±1.5 percent, data obtained with poor sensitivity. Although the results of the gross binocular tests were gratifying, stereoscopic sensitivity to finer details was poor.

In this case the lower visual acuity of the right eye and the poor stereopsis could well

be reasons for the ability of this patient to wear a unilateral contact lens with comfort, in spite of the difference in magnification of the images between the eyes.

CASE 6

A 55-year-old man had correctible visual acuity of 20/100 in the right eye and 20/30— in the left eye. Because of the nature of his work, he was extremely desirous of obtaining better binocular function. An intracapsular cataract extraction was performed on the right eye. The prescription for spectacles at that time was +11.0D. sph. ⌒ −3.25D. cyl. ax. 95° for the right eye and plano for the left eye; with this correction he obtained visual acuity of 20/20 in the right eye and 20/30— in the left eye. Approximately a year later he was fitted with a corneal contact lens. Visual acuity in the right eye with the contact lens was 20/20. The results of the space-eikonometer measurements were: axis 90°: L, 7.5 ±0.75 percent; axis 180°: L, 8.0 ±1.0 percent. At this time the patient could wear the lens about six hours daily but the eye was easily irritated.

The reduced visual acuity of the patient owing to early cataract in the left eye was felt to be a definite factor in the patient's ability to tolerate the magnification difference so readily, except for the irritability.

CASE 7

A 67-year-old man who had had an intracapsular cataract extraction from the left eye three years prior to examination had worn a corneal contact lens since a few months after operation. Visual acuity of the left eye with the contact lens was 20/20 and that of the right eye with a spectacle correction of +3.12D. sph. ⌒ −0.62D. cyl. ax 90° was 20/25. The contact lens was worn comfortably 12 or more hours daily, the only symptoms being that objects seemed larger or nearer when the left eye alone was used. The results of the space-eikonometer measurements were: axis, 90°: R, 6.0 ±0.5 percent; axis 180°: R, 5.5 ±0.75 percent.

This patient had the least difference in magnification between the images of any of the group studied, perhaps because the eyes were basically axially hyperopic. The slightly reduced acuity of the phakic eye also may have been an important factor in his ability to tolerate this difference in magnification of the images.

COMMENT

A study is being made to obtain more definite insight into the problem of how patients tolerate a significant amount of residual aniseikonia when the aphakic eye in unilateral aphakia is corrected by a corneal contact lens. Only a partially objective answer is to be found in the seven cases reported briefly herein. Previous reports have dealt primarily with subjective responses of the patient because, from the point of view of the clinician, this is the most important aspect of the correction. Furthermore, subjectively, most of our patients expressed no great difficulty in wearing the corrections.

It would seem questionable that a true decrease in corneal sensitivity plays a role, since in most of our cases only needling operations were performed. However, motivation may indeed compel the patient to make a great effort to succeed in wearing a contact lens. It is quite likely that motivation plays a definite role in the length of time a contact lens can be worn, for this was especially noticeable in the young patients in our group; they seemed to adapt quickly and to ignore the lens after a few months. We cannot ignore the problems of the subjective decrease in corneal sensitivity and the role that motivation on the part of the patient plays, for these may be chiefly responsible for the tolerance to the wearing of the contact lenses. There can be little doubt that oftener than not the answer of the patient to the effect that he wears the lens with comfort refers specifically to these two aspects of the problem rather than to his reaction to binocular function which may be impaired.

Gross testing of fusion by the synotophore, for example, on several of these patients did indeed show some binocular function, but the patients were not sensitive to the fine stereoscopic task demanded on the space-eikonometer, nor were they able to respond normally on the horopter instrument which shows the presence of normal stereoscopic spatial localization.

The brain may well learn to reinterpret spatial characteristics in the presence of a difference in the magnification of the images in the two eyes and this may lead to new innervations for co-operative movements of

the eyes; but the fact that such changes may have occurred does not mean necessarily that normal binocular vision has been restored. This is borne out by the fact that the eikonometer examination will give essentially the same result after the contact lens has been worn for a long time as before it is worn.

While a lower visual acuity in one eye and a basic lack of stereopsis may provide a way of explaining the tolerance of some of our patients to the residual aniseikonic errors when the acuity is equally good in the two eyes and stereopsis is present in the space-eikonometer, we need to consider other aspects of the main problem. These may lie in the reasoning emphasized by Linksz,[2] in which we would infer that only small aniseikonic errors can lead to discomfort. For differences in image magnification greater than about five percent, binocular vision and binocular co-ordination would be impaired, save in the macular areas alone. Physiologically these differences would interfere greatly with (1) stereoscopic spatial localization and (2) fusion and fusional movements, since corresponding images in the two eyes, especially in the peripheral regions, will lie outside Panum's areas of fusion, and innervations for a fusional movement would be opposite in sign for images on opposite sides of the foveas. Prism vergences would be reduced accordingly.[5]

In these two phenomena lies the basis for the reasoning that patients with moderately large aniseikonic errors tend to suppress or abandon normal binocular vision in the greater part of the binocular visual field, save perhaps in the macular areas. Even in these, the binocular function must be greatly reduced when the difference in magnification of the images in the two eyes is large, as in the correction of unilateral aphakia with spectacle lenses where the aniseikonia may exceed 30 percent. Evidence for this reasoning also lies in the fact that rarely are found patients who seem to have normal binocular vision with aniseikonic errors greater than five to six percent.

In the seven patients whose cases are reported, the lower visual acuity could have occurred in the phakic eye, usually owing to early opacity of the lens, or in the aphakic eye, owing to a poor fitting of or to errors in the contact lens. Partial suppression of the aphakic eye may be related to the fact that the cataract had been present for several years prior to its extraction.

Summary

A study is reported of seven patients who were wearing a contact lens for the correction of an aphakic eye in unilateral aphakia; each had had eikonometer measurements and, when possible, other spatial localization tests. The results of the eikonometer examination showed that in all cases there was a residual aniseikonic error of 5.5 to 9.0 percent. No patient reported discomfort in wearing the contact lens. The results were considered from the point of view of the decrease in corneal sensitivity, the role of motivation to succeed in wearing the lenses, the lowered visual acuity in one eye (five patients showed lowered visual acuity), the loss of other than gross stereopsis (four patients showed this loss, or decreased sensitivity), and suppression of one image by the aphakic eye due to long disuse. The basis for reasoning that there would be an impairment of binocular vision in patients for whom the aniseikonic errors were greater than six percent was pointed out by showing how these patients avoided the influence of the aniseikonic error.

The Mayo Clinic.

References

1. Ogle, K. N., Burian, H. M., and Bannon, R. E.: On the correction of unilateral aphakia with contact lenses. A.M.A. Arch. Ophth., **59**:639-652 (May) 1958.

2. Linksz, A.: Aniseikonia: With notes on the Jackson-Lancaster controversy. Tr. Am. Acad. Ophth., **63**:117-140 (Mar.-Apr.) 1959.

3. Ogle, K. N.: Researches in Binocular Vision. Philadelphia, Saunders, 1950, p. 20.
4. ———: Researches in Binocular Vision, Philadelphia, Saunders, 1950, p. 153.
5. Ellerbrock, V. J.: The effect of aniseikonia on the amplitude of vertical divergence. Am. J. Optometry, **29**:403-415 (Aug.) 1952.

SECONDARY CORNEA GUTTATA*

A LATE CHANGE IN LUETIC INTERSTITIAL KERATOPATHY

J. REIMER WOLTER, M.D.
Ann Arbor, Michigan

In a recent paper[1] was demonstrated a new type of cornea guttata found in old cases of interstitial keratopathy which we called secondary cornea guttata. Secondary cornea guttata exhibits hyaline excrescences (guttae) on the posterior surface of Descemet's membrane in a very peculiar arrangement of lines and geographic patterns of confluent guttae. In this earlier paper we compared the changes of secondary cornea guttata with those of primary cornea guttata of Fuchs' endothelial and epithelial dystrophy. It was concluded that secondary cornea guttata probably represents endothelial pathology which is secondary to old interstitial keratopathy found in all our cases and which is related to primary cornea guttata.

The present paper represents the histologic demonstration of two more cases of secondary cornea guttata in old luetic keratopathy.

FIRST CASE

This 37-year-old white woman was first seen in this Eye Clinic on August 18, 1959. Her family history was negative except for the fact that her parents had lues. The patient gave a history of a binocular inflammation and virtual blindness at the age of five years which was then diagnosed and treated as luetic interstitial keratopathy. She received at that age treatment with a series of injections. Her eye sight slowly improved but never became quite normal again. Blood and spinal fluid were examined for syphilis in 1949 and were found to be negative. She never received further antiluetic treatment.

On August 3, 1959, she came to Dr. J. W. Henderson of this Eye Clinic asking whether a corneal transplant could be done to improve her vision. The eye examination at this time revealed her vision to be: O.D., 20/80; O.S., 20/70. The eyes were straight in primary position and the extraocular muscle function was full. The slitlamp examination revealed both corneas to contain many deep ghost vessels some of which still contained blood. There also was deep scarring of the corneal stroma O.D. more than O.S. The anterior chamber was clear, O.U. One old posterior synechia was seen temporally on the iris of the left eye. The intraocular pressure was 10.9 mm. Hg, O.U. The lens appeared clear, O.U. The fundus was seen only in a haze because of the corneal opacities but no fundus pathology was seen.

The diagnosis of inactive interstitial keratopathy, O.U., and old inactive iritis, O.S., was made. A penetrating keratoplasty was performed by Dr. Henderson on September 3, 1959. The removed button of central cornea of the patient measuring 6.5 mm. in diameter was immediately fixed in ammonium bromide formalin for histologic examination. The graft is now well healed and has as yet remained clear.

METHOD OF HISTOLOGIC EXAMINATION

Flat sections were made of the two corneal buttons (Case 1 and Case 2) on the freezing microtome. These sections were stained with the "panoptic" technique of the silver carbonate methods of del Rio Hortega as described by Scharenberg and Zeman.[2]

All illustrations of this paper are unretouched photomicrographs.

HISTOLOGIC FINDINGS IN CASE 1:

The corneal epithelium was about normal. Many nerve fibers were seen to enter the epithelial layer (fig. 1). They branched and could be seen to enter epithelial cells with their final branchings. Bowman's membrane was continuous and of about normal thickness. The corneal stroma was somewhat irregular in its architecture but there was no

* From the Department of Ophthalmic Surgery, The University of Michigan.

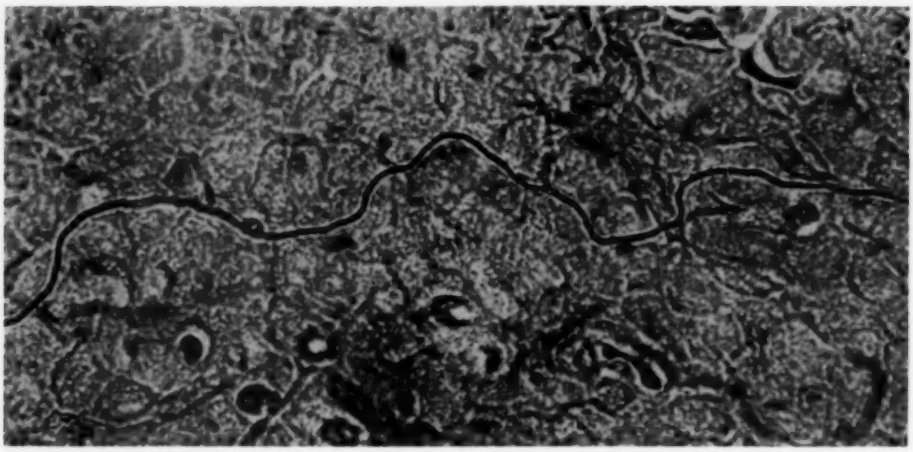


Fig. 1 (Wolter). *Case 1,* nerve fiber in the corneal epithelium. (Frozen section, panoptic technique of del Rio Hortega, photomicrograph.)

cellular infiltration. Many thin-walled blood vessels were seen in the deep stroma. Some of these blood vessels showed a narrow empty lumen (fig. 2). Others contained some leukocytes (fig. 3) and others contained rolls of erythrocytes (fig. 4). Many of the blood vessels were found directly on the inner (anterior) surface of Descemet's membrane.

The outstanding findings in this study were seen in the layers of Descemet and the endothelium of this corneal button. The endothelium was atrophic in most areas (fig. 5). Many hyaline excrescences on the inner surface of Descemet's membrane were found virtually all over the corneal button. These hyaline excrescences were found to protrude into and through the endothelial

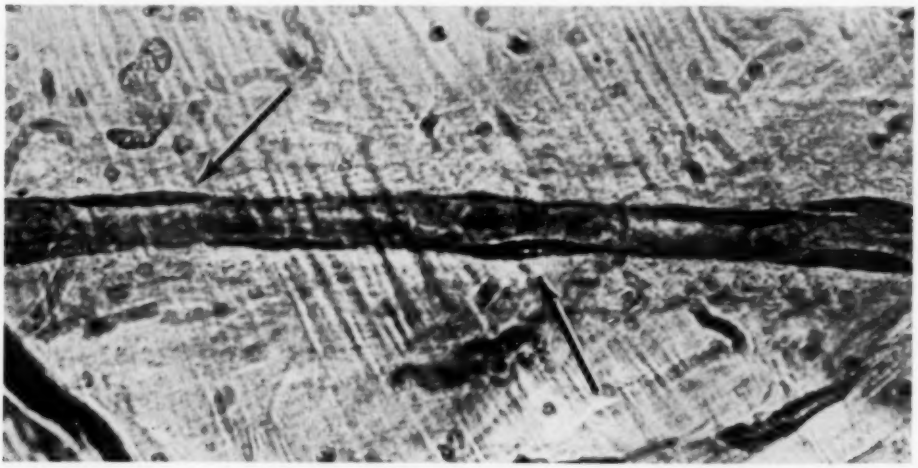


Fig. 2 (Wolter). *Case 1,* a thin deep ghost vessel with empty lumen in the corneal stroma. The endothelial nuclei can be seen (arrows). (Frozen section, panoptic technique of del Rio Hortega, photomicrograph.)

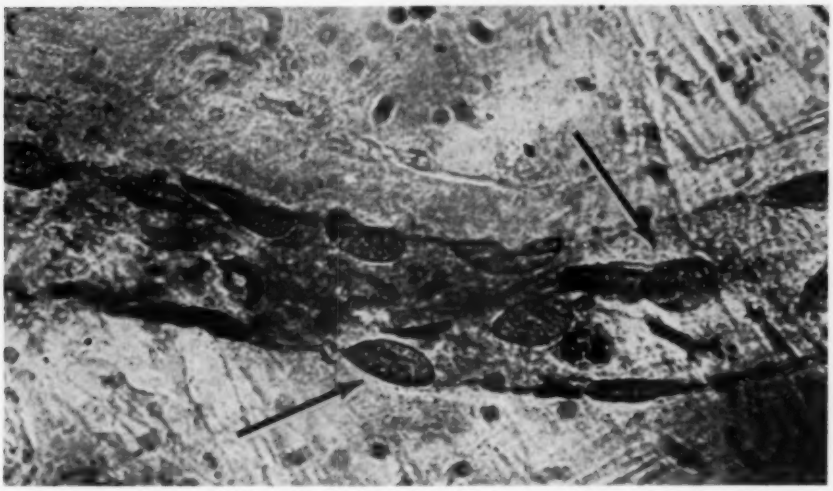


Fig. 3 (Wolter). *Case 1,* a larger deep ghost vessel containing polymorphonuclear cells. The endothelial nuclei can be seen (arrows). (Frozen section panoptic method of del Rio Hortega, photomicrograph.)

layer (figs. 6 and 7). They were round and showed a very definite lamellation. It could be observed that these hyaline bodies had pushed aside the endothelial nuclei which were often seen piled up around densely arranged hyaline excrescences (figs. 6, 8, and 9). In many areas it could be observed that hyaline excrescences had become confluent

Fig. 4 (Wolter). *Case 1,* two thin-walled ghost vessels of the deep corneal stroma. Erythrocytes are seen in the lumen (arrows). (Frozen section, panoptic technique of del Rio Hortega, photomicrograph.)

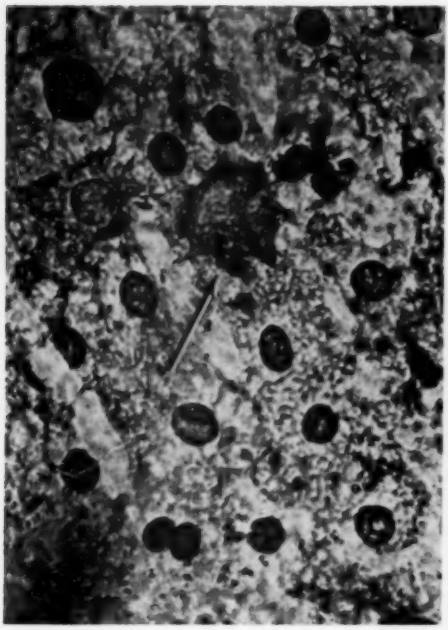


Fig. 5 (Wolter). *Case 1,* an area of corneal endothelium in a flat section. The cellular nuclei are scarce and irregular in size and shape. One endothelial cell shows a late stage of atrophy (arrow). (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

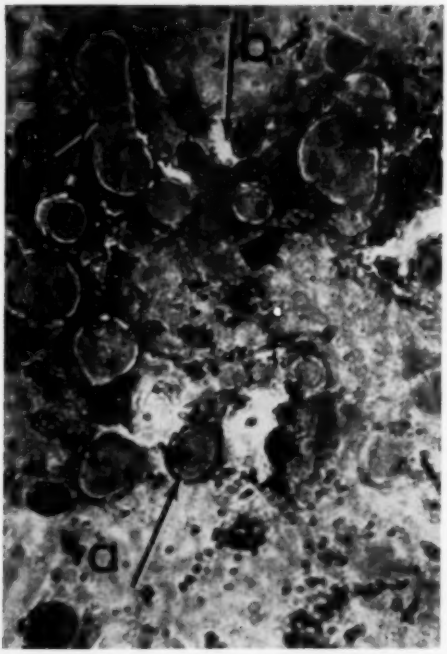


Fig. 6 (Wolter). *Case 1,* an area of the endothelium in a flat section. Many hyaline excrescences are seen in it (a). The endothelial nuclei are pushed aside by the hyaline guttae (b). Three hyaline guttae have become confluent and form a short line (c). (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

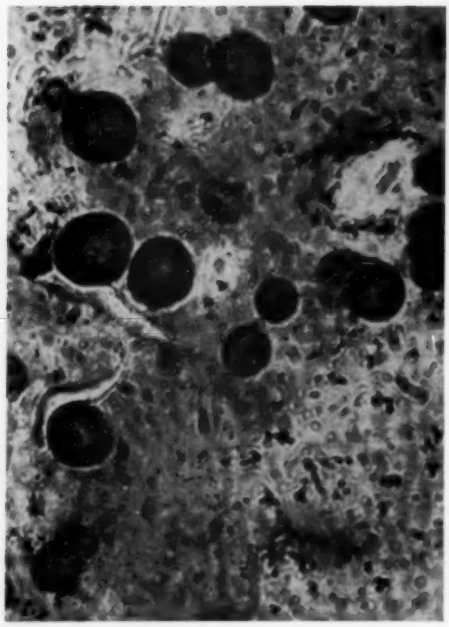


Fig. 7 (Wolter). *Case 1,* a group of single hyaline guttae on the posterior surface of Descemet's membrane seen in a flat section. The endothelium of this area is lost. (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

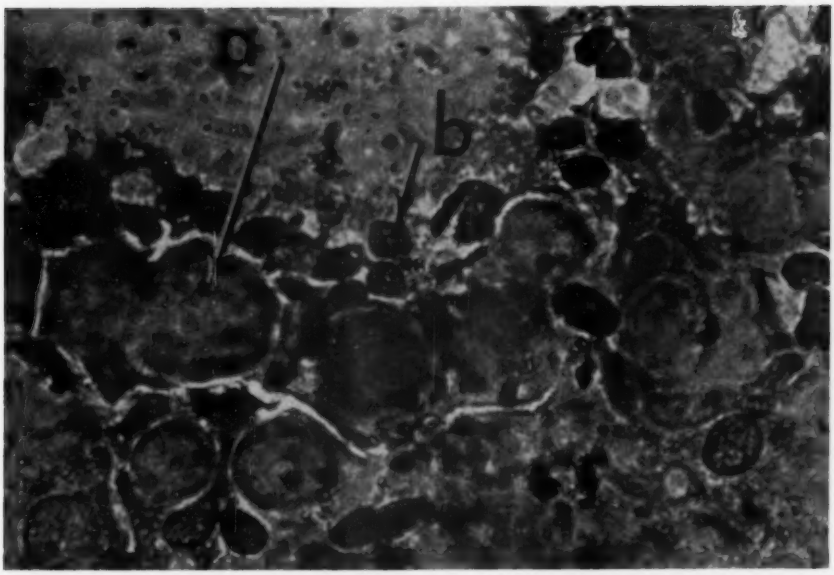


Fig. 8 (Wolter). *Case 1,* high-power view of a line of hyaline excrescences on Descemet's membrane (a). The endothelial nuclei are pushed aside and can be seen around the guttae (b). (Frozen flat section, panoptic method of del Rio Hortega, photomicrograph.)

with each other and thus formed lines or geographic patterns (figs. 8 to 12). It was obvious that all these lines and figures were composed of guttae which had become confluent. In some of the thicker sections we were able to see that these lines of hyaline bodies on the posterior surface of Descemet's membrane were running the same course as the ghost vessels on the anterior surface of Descemet's membrane. However, we were not able to demonstrate this relation of the lines of guttae to the deep vessels of the stroma in a photograph.

Second case

This 37-year-old white man was first seen on November 9, 1958, in this Eye Clinic. He gave a history of having had good vision in both eyes until about 20 years ago. Both eyes—one after another—became red and inflamed at that time and the vision decreased. A doctor who treated the eye disease told the patient that this was inherited from his parents. The patient received a general treatment with series of injections for about one year. He had negative serology at the time of this examination.

The eye examination revealed his vision to be: O.D., counts fingers at five feet; O.S., 20/200. The external examination revealed normal findings. The patient had a saddle nose. He had lost all his teeth. At the slitlamp his right eye showed the cornea to be fairly clear in its periphery. The corneal center, however, showed thickening, deep scarring, deep ghost vessels and a very marked endothelial irregularity. The anterior chamber appeared optically empty. The lens was clear. The fundus was not very well seen but appeared normal. The slitlamp examination of the left eye showed much less corneal scarring. However, there were also many deep ghost vessels and some endothelial changes. The latter were composed of guttae on the posterior surface of the cornea. Many of these guttae were seen to be arranged in lines and geographic patterns. All these changes were seen in the central cornea while the corneal periphery was relatively clear. The other parts of the left eye were normal. The intraocular pressure was 17.3 mm. Hg, O.U.

The clinical diagnosis in this case was: Old interstitial keratopathy with secondary cornea guttata, O.U.

A penetrating keratoplasty, O.D., was performed on September 2, 1959. The removed corneal button measuring 7.0 mm. in diameter was immediately fixed for histologic examination.

Histologic findings in Case 2

The superficial layers of the cornea looked

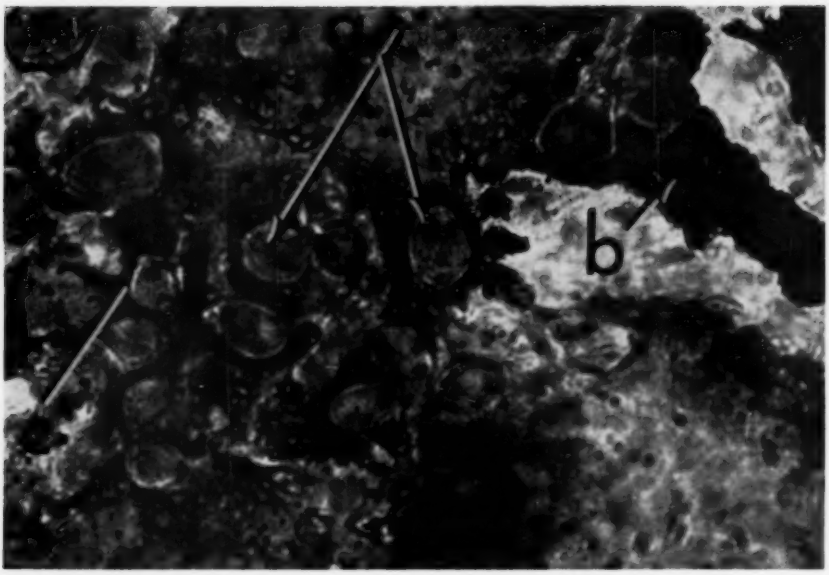


Fig. 9 (Wolter). *Case 1,* another group of hyaline excrescences (a) on the posterior surface of Descemet's membrane some of which (b) have formed a branching line. Endothelial cells are seen among the guttae (c). (Frozen flat section, panoptic method of del Rio Hortega, photomicrograph.)

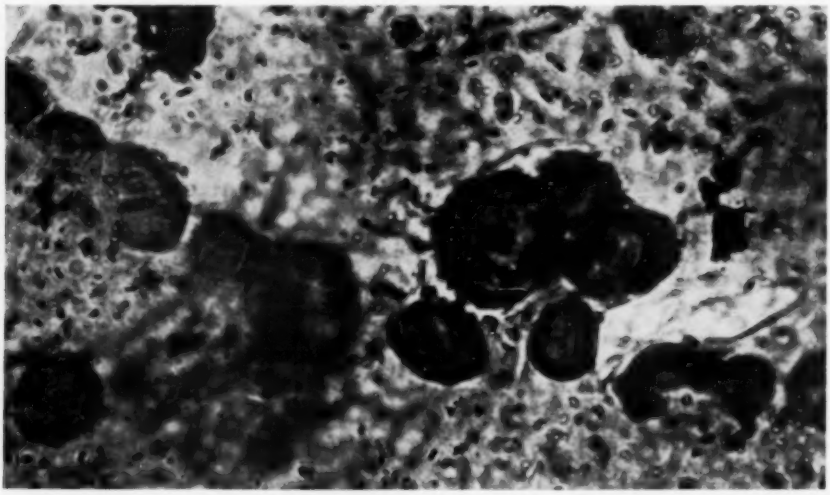


Fig. 10 (Wolter). *Case 1,* a row of hyaline excrescences on the posterior surface of Descemet's membrane. The endothelium of this area was lost. (Frozen flat section, panoptic method of del Rio Hortega, photomicrograph.)

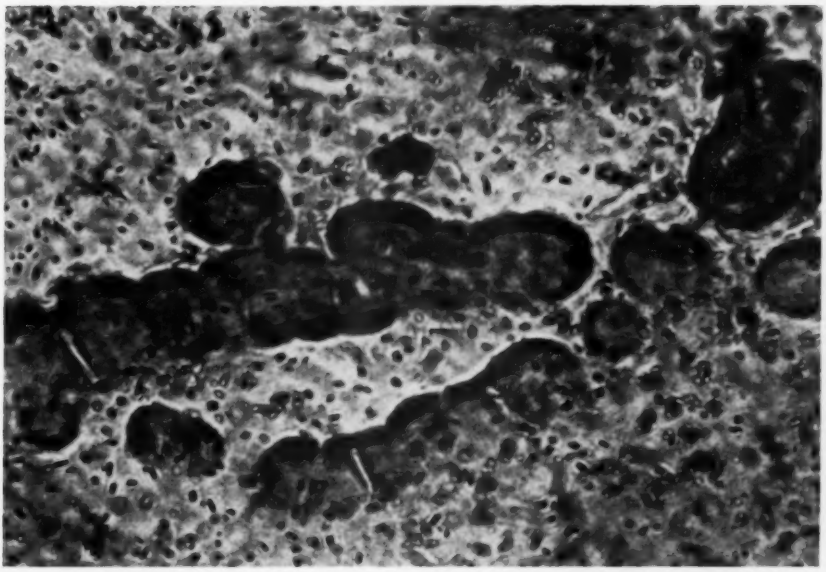


Fig. 11 (Wolter). *Case 1,* branching pattern of confluent hyaline guttae on the posterior surface of Descemet's membrane in a flat section. (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

virtually normal except for a certain irregularity of the stromal lamellae. Many ghost vessels were seen in the deep stroma. Descemet's membrane was wrinkled and it was therefore difficult to get good flat sections of this membrane and the endothelium. Figure 13 shows a flat section through the wrinkled membrane of Descemet. Many hyaline ex-

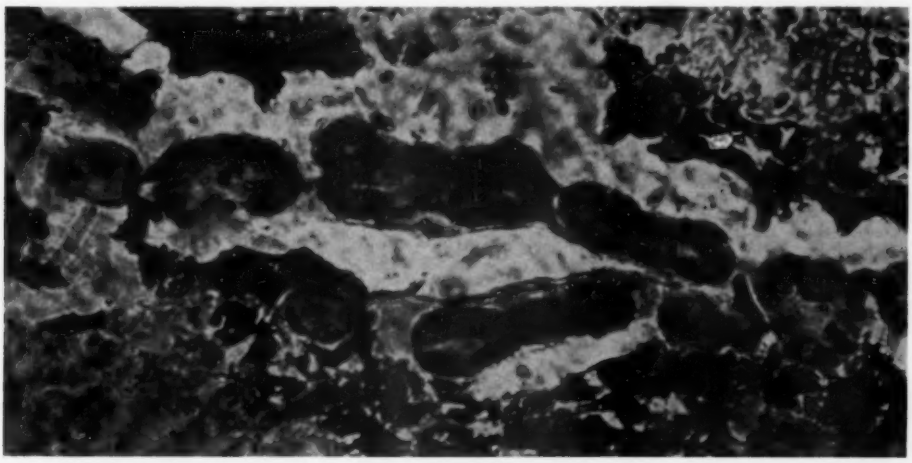


Fig. 12 (Wolter). *Case 1,* two branching rows of confluent hyaline guttae on Descemet's membrane. The shrunken endothelium is stained very dark and can be seen around the rows of guttae. (Frozen flat section, panoptic method of del Rio Hortega, photomicrograph.)

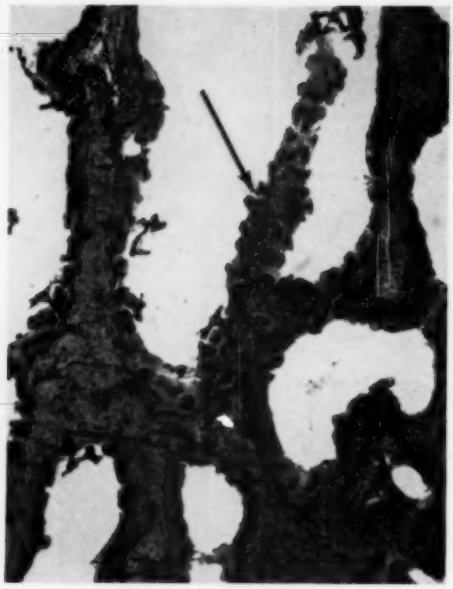


Fig. 13 (Wolter). *Case 2,* low-power view of a flat section through the wrinkled membrane of Descemet. Many guttae are seen on the posterior surface of this membrane. The endothelium is lost. (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

crescences are seen on the inner surface of this membrane. In many areas these hyaline excrescences formed rows (figs. 14 and 15). In some areas complicated geographic configurations were seen (fig. 16). All the formations were composed of round hyaline bodies. Most of the corneal endothelium was lost in this case. In some areas, however, it was seen and appeared atrophic (fig. 14).

Discussion

The two cases of old inactive interstitial keratopathy presented in this paper showed a peculiar type of cornea guttata with formation of lines and geographic patterns. In one of the cases it could be demonstrated in

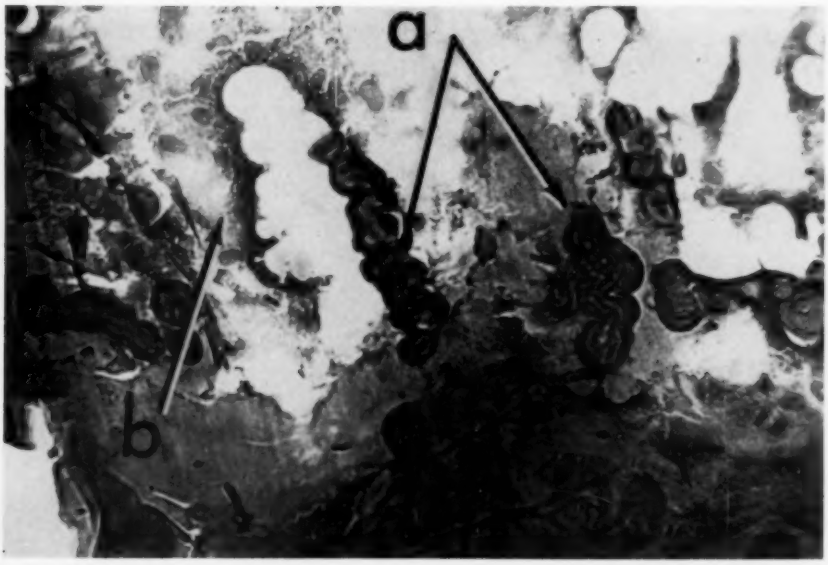


Fig. 14 (Wolter). *Case 2,* high-power view of some short rows of confluent guttae on Descemet's membrane (a). The atrophic endothelium is stained only very slightly (b). (Frozen flat section, panoptic technique of del Rio Hortega, photomicrograph.)

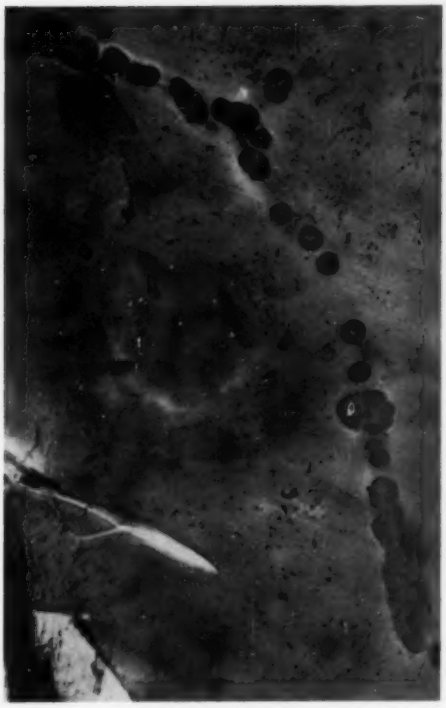


Fig. 15 (Wolter). *Case 2,* a row of hyaline guttae on the posterior surface of Descemet's membrane in a flat section. The endothelium is lost in the histologic process. (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

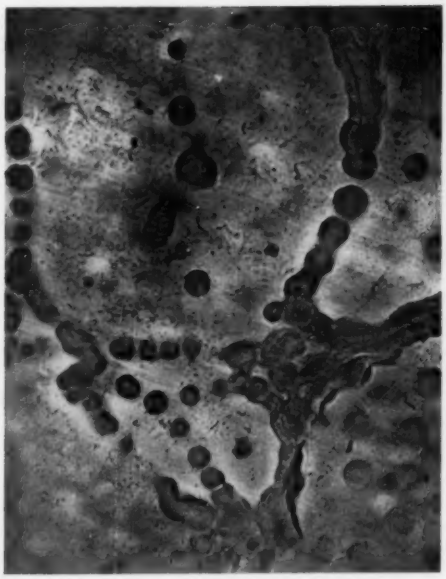


Fig. 16 (Wolter). *Case 2,* geographic pattern of partly confluent guttae on the posterior surface of Descemet's membrane in a flat section. (Frozen section, panoptic method of del Rio Hortega, photomicrograph.)

thick sections that the lines of guttae on the posterior surface of Descemet's membrane run parallel to deep ghost vessels on the other side of Descemet's membrane. A third histologic and three clinical cases of the same change were described recently.[1] The occurrence of this type of cornea guttata is considered secondary to luetic interstitial keratopathy. We therefore call it secondary cornea guttata. It must be emphasized that not all guttae in these cases are arranged in lines or patterns. In many areas the distribution and type of hyaline excrescences are exactly that seen in Fuchs' endothelial and epithelial dystrophy. In many cases of primary cornea guttata of Fuchs' dystrophy, however, I have never seen the occurrence of confluent guttae forming lines and patterns which is typical for secondary cornea guttata.

Summary

Two more cases of secondary cornea guttata in old luetic interstitial keratopathy are demonstrated histologically. The typical feature of secondary cornea guttata is that the hyaline excrescences form lines and geographic patterns which run parallel to deep stromal ghost vessels.

Eye Clinic,
University of Michigan Medical Center.

References

1. Wolter, J. R., and Larson, B. F.: Pathology of cornea guttata. Am. J. Ophth., **48**:161 (July, Pt. II) 1959.

2. Scharenberg, K., and Zeman, W.: Zur Technik und zur Leistungsfaehigkeit der Hortega'schen Silberkarbonatmethoden. Arch. Psychiat., **188**:430, 1952.

OCULAR CHANGES RELATED TO ENDOCRINE DYSFUNCTION*

With emphasis on ocular complications in thyrotoxicosis

Richard O. Schultz, M.D., Henry E. Hamilton, M.D., and Alson E. Braley, M.D.
Iowa City, Iowa

Introduction

The division of endocrine exophthalmos into either pituitary or thyroid types[1] has led to considerable controversy and contradiction regarding the role that each gland may have in this disorder. In addition, the term exophthalmos is frequently used in reference not only to protrusion of the eye but also to the complex of eye signs which may accompany proptosis.

Analysis of a large group of patients with thyroid dysfunction clearly shows that the endocrine eye lesion accompanying Graves' disease consists of much more than simply exophthalmos, and that associated changes do not necessarily coincide in severity with the degree of exophthalmos.[2] These other components of the eye lesion may, in themselves, be of greater clinical concern to both the ophthalmologist and the patient. The gross components of the eye lesion in thyrotoxicosis consist of proptosis, ophthalmoplegia, lid retraction, and periorbital swelling.[2] If one observes these components separately, it becomes obvious that any one of them may dominate the clinical illness and pursue a course which is quite independent of the others. Since thyrotoxicosis itself is probably a result of multiglandular dysfunctions, it seems reasonable to consider that the accompanying eye signs may be influenced by multiple endocrine factors.

Any of these components of the endocrine eye lesion can occur in either patients with thyrotoxicosis or in those without evidence of classical Graves' disease. Therefore, the division of exophthalmos into pure pituitary and pure thyroid types becomes an oversimplification. Indeed, simply because a patient with exophthalmos fails to manifest clinical hypermetabolism does not eliminate the thyroid gland from contributing to the eye problem. And, likewise, if a patient has thyrotoxicosis with ocular changes, the pituitary gland may still play a dominant role in the ophthalmopathy. As Brain has suggested: "We would be wise to be content with the term 'endocrine exophthalmos' until we know more about it."[3]

It is the purpose of this paper to describe the ocular changes in 165 patients with thyrotoxicosis after I^{131} therapy and compare them to ocular changes with characteristics of the endocrine eye lesion noted in a small group of patients without clinical hypermetabolism. The division of the thyrotoxic from the nonthyrotoxic patient should not be interpreted as being of significance in the etiology of endocrine exophthalmos but it is of significance in the clinical management of these patients.

Methods of study

Patients in this study were referred for thyroid evaluation to the thyroid clinic at the State University of Iowa. The ocular changes in thyrotoxicosis were observed in a group of 165 patients who were selected only because of signs and symptoms of thyrotoxicosis, and not with regard to ocular complications.[2] The nonthyrotoxic group on the other hand were evaluated because their ocu-

* From the Department of Ophthalmology and the Thyroid Clinic of the College of Medicine, State University of Iowa, University Hospitals. Members of Thyroid Clinic: E. L. DeGowin, H. E. Hamilton and R. E. Hodges (Internal Medicine), T. C. Evans (Radiation Research Laboratory), D. Alftine and H. B. Elkins (deceased) (Radiology), R. O. Schultz (Ophthalmology), J. A. Buckwalter and E. E. Mason (Surgery).

lar problem was suspected to be of endocrine origin. All thyrotoxic patients were previously untreated. The diagnosis of thyrotoxicosis was based upon the I^{131} uptake at four and 24 hours, the protein-bound iodine value, results of the basal metabolism rate and upon the clinical judgment of the members of the thyroid clinic. The only form of antithyroid therapy used was I^{131}. Patients were re-examined at three-month intervals and treated until thyroid function was controlled.

Patients were questioned about eye symptoms at each visit and photographs of eye signs were obtained in many cases. A Hertel-type prism exophthalmometer was used (Krahn, Hamburg). Base readings were kept constant. The readings were all obtained at the same time of day by the same examiner. Individual records were kept for each visit and transferred to key-sort punch cards for analysis.

Results

Patients (165) with thyrotoxicosis. In this group there were 27 men and 138 women with an age range of nine to 80 years. Of these, 90.9 percent had plasma protein-bound iodine determinations above 8.0 μg./100 ml. and 91.5 percent initially had a thyroidal uptake of radioactive iodine greater than 40 percent in 24 hours. Twenty-three percent of the patients had some form of skeletal myopathy. Approximately 14 percent had ophthalmoplegia. Pretibial myxedema was observed in 3.0 percent of all patients. Using an average single dose of 4.6 mc. of I^{131}, 57.5 percent of the patients were controlled with one dose, 30.3 percent required two doses, and 18.2 percent received three or more doses.

Incidence

Of the 165 patients with thyrotoxicosis, two-thirds showed one or more of the components of the endocrine eye lesion exclusive of increases in proptosis, that is, either ophthalmoplegia, lid retraction or periorbital swelling (table 1). Signs and symptoms were present in 120 patients or 73 percent. Of these 120, 15 percent were judged to have severe disability, 39 percent were of moderate severity, and 44 percent were considered of minor significance. While the ratio of women to men was five to one, with respect to the incidence of thyrotoxicosis, the eye lesion was found in 71.5 percent of the women and 71.6 percent of the men patients.

Effects of I^{131} on the eye lesion (table 2). All patients were euthyroid after treatment and followed for at least one year before they were included in this study. In Table 2, increases in proptosis were tabulated separately from the other components of the eye lesion for comparison in response to I^{131} therapy.

Proptosis. Proptosis increased 1.5 mm. or more in 65 percent of patients showing signs of the endocrine eye lesion and remained the same in 26.5 percent. In the group of 45 patients without signs or symptoms, exophthal-

TABLE 1

INCIDENCE OF EYE SIGNS IN 165 PATIENTS WITH THYROTOXICOSIS (EXCLUDING PROPTOSIS)

	Before I^{131} Rx	Disappeared	Residual	No Improvement
Lid retraction	82	56	23	3
Periorbital edema	67	45	15	7
Ophthalmoplegia	23	11	8	4
Total no. patients with one or more eye signs	110			

TABLE 2

EFFECT OF I^{131} ON THE ENDOCRINE EYE LESION IN 165 PATIENTS WITH THYROTOXICOSIS

A. Signs and Symptoms Following I^{131} Rx

	Disappeared	Residual	No Improvement
120 patients with signs of: lid retraction, periorbital edema, ophthalmoplegia, symptoms	55	58	7
	45.8%	48.3%	5.8%

10 patients had symptoms with no signs

B. Proptosis Following I^{131} Rx

	Decreased	Same	Increased
120 patients with eye signs and symptoms	10	32	78
	8.4%	26.6%	65%
45 patients with no eye signs or symptoms	2	36	7
	4.4%	80.0%	15.6%

mometric readings showed an increase of 1.5 mm. or more in only 15.6 percent and remained the same in 80 percent. In both groups, that is, with and without eye signs, a total of 51.5 percent of all the patients showed an increase in proptosis following treatment with I^{131}. Aside from the increase in proptosis, control of thyrotoxicosis with I^{131} resulted in improvement in the eye lesion in 106 of the 120 patients affected. Seven patients in this group became significantly worse.

Alleviation of symptoms, such as pain, tearing, burning, diplopia, and blurred vision, coincided with reduction of periorbital edema, muscle paresis and lid retraction, in spite of a measured increase in proptosis. Only nine percent of patients retained significant symptoms or signs after their toxicity was controlled, while proptosis either remained the same or increased in 91.5 percent. The average exophthalmometric reading for the patient with eye signs who was treated with I^{131} was 17.5 mm. compared to 14.7 mm. for the patient with no ocular complications.

In this series of patients with thyrotoxicosis, even though the eyes may have moved forward as much as 8.0 mm. during treatment, the maximum difference between O.D and O.S was never at any one time greater than 2.5 mm.

Ophthalmoplegia. This aspect of the endocrine eye lesion will be discussed in detail with electromyographic analyses in a separate publication.[4] Fourteen percent of the 165 patients with thyrotoxicosis showed gross ophthalmoplegia. Approximately 50 percent of these showed complete return of extraocular muscle function when thyrotoxicosis was controlled. The superior rectus and inferior oblique muscles were involved in almost all instances.

Associated skeletal myopathy. Of the total 165 patients, 38 had varying degrees of muscle weakness involving shoulder girdle, thigh or calf. Of this group 33 (87 percent) had eye signs compared to the over-all incidence of 73 percent of the total group of 165 patients.

Associated pretibial myxedema was found in five patients and each not only had some component of the eye lesion but all five still had significant eye disability after control of toxicity. The value of pretibial myxedema as a prognostic sign has been emphasized previously.[5]

Fig. 1 (Schultz, Hamilton and Braley). A 63-year-old thyrotoxic woman. (a) Demonstrating the periorbital component of the endocrine eye lesion before treatment with I^{131}. (b) Appearance following I^{131} therapy.

Case reports

The following cases are presented to illustrate predominance of one of the components of the endocrine eye lesion. As noted in the histories and photographs, these patients usually demonstrated proptosis either initially or subsequent to treatment with I^{131}, in addition to other ophthalmopathy. The first four patients all had thyrotoxicosis.

Case 1

This 63-year-old woman developed signs and symptoms of thyrotoxicosis in June, 1956. I^{131} uptakes were 81 and 77, protein-bound iodine, 14.6, and basal metabolism rate, +55. She received three doses of I^{131} from July, 1956, to October, 1956 (average dose of 3.0 mc.). By February, 1957, she clinically appeared euthyroid with laboratory values of I^{131} 18-33, protein-bound iodine, 5.4 and basal metabolism rate, +1.0. Figure 1-a shows the appearance of the patient. Figure 1-b was taken after treatment with I^{131}. This patient displayed primarily periorbital edema, although there was an increase in exophthalmometric readings of 3.0 mm., O.U., after I^{131} was given.

Fig. 2 (Schultz, Hamilton and Braley). A 73-year-old woman who has had marked proptosis for 27 years following treatment for "exophthalmic goiter." Recent examination reveals normal visual function.

Fig. 3 (Schultz, Hamilton and Braley) A nine-year-old thyrotoxic girl who illustrates primarily the lid retraction component of the endocrine eye lesion.

Case 2

This 73-year-old woman (fig. 2) was treated for "exophthalmic goiter" by subtotal thyroidectomy in 1932. Two years preceding this surgery, she had classic signs of Graves' disease with proptosis and swelling around both eyes. This patient's exophthalmometer readings remained at 25.0 mm. O.U. for 26 years. Recent examination revealed no corneal changes, 6/9+ central acuity, O.U. with normal visual fields. At the present time, she illustrates proptosis without evidence of other ocular changes related to endocrine dysfunction.

Case 3

This nine-year-old girl (fig. 3) developed signs and symptoms of thyrotoxicosis in May, 1958, with unilateral lid retraction and apparent proptosis. I^{131} uptakes done in September, 1958, were 24 and 51. Exophthalmometer readings were 20 and 18. Ocular motility was normal, and there was no evidence of edema. This patient appears to show primarily unilateral lid retraction. However, the exophthalmometer readings would suggest bilateral exophthalmos for a patient this age.

Case 4

This 58-year-old woman illustrates both the ophthalmoplegic and proptosis components of the endocrine eye lesion (fig. 4). She developed signs and symptoms of thyrotoxicosis in December, 1955, and simultaneously displayed signs of extraocular muscle weakness and proptosis. Initial readings were 26 mm., O.D., and 27 mm., O.S., which increased

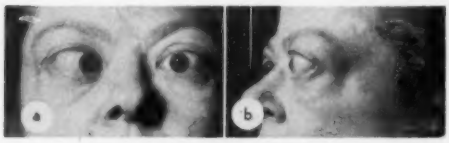


Fig. 4 (Schultz Hamilton and Braley). A 58-year-old thyrotoxic woman, illustrating the ophthalmoplegic component of the endocrine eye lesion.

to 28 mm., O.D., and 28 mm., O.S., following two doses of I^{131}. Her toxicity was controlled by radioactive iodine. The proptosis and ophthalmoplegia have persisted.

Endocrine eye lesion in patients without thyrotoxicosis. During the same period that the previous group of 165 thyrotoxic patients were being studied, 16 patients who did not show evidence of hyperthyroidism were examined because of ocular changes similar to those of the endocrine eye lesion associated with Graves' disease. Several points are immediately outstanding when comparing these patients to those with thyrotoxicosis.

Werner's test. Fourteen of the 16 patients failed to show a normal suppression of I^{131} uptakes after tri-iodothyronine (positive Werner's test) suggesting an endocrine abnormality.

Unilateral changes. Endocrine eye lesions, which were predominately unilateral, were usually confined to this nontoxic group of patients. Patients in this category were observed to have differences as great as 8.0 mm. between O.D and O.S, while as previously stated, none of the thyrotoxic patients showed a difference greater than 2.5 mm. Not only is the proptosis unilateral but frequently all the ocular changes are seemingly limited to one eye. However, the apparently "uninvolved eye" may show an exophthalmometric reading greater than normal even though other components of the eye lesion are lacking in this eye. In all, nine of the 16 patients showed changes essentially confined to one eye.

Ophthalmoplegia in this group of patients was usually more severe than in patients with thyrotoxicosis. However, it is interesting to note that in some instances an eye could protrude 6.0 mm. without any gross evidence of impaired motility. Seven patients of this nonthyrotoxic group showed evidence of extraocular muscle paresis.

Unilateral lid retraction was a common finding in patients with a positive Werner's test and did not necessarily correlate with the amount of proptosis. In the nontoxic patient with unilateral exophthalmos, lid retraction and ophthalmoplegia frequently are the major points of concern both from a cosmetic and symptomatic standpoint. In attributing unilateral exophthalmos to endocrine dysfunction, the Werner's test can be extremely helpful. In the absence of a positive Werner's test, many other causes of unilateral proptosis must be excluded and sometimes the diagnosis can only be made by evaluating the response to therapy.

The endocrine eye lesion can occur bilaterally in patients without evidence of Graves' disease, as illustrated in Case 5, Figure 5. In fact, this patient displayed the most severe complications of the endocrine eye lesion seen in the entire group.

CASE 5

A detailed past history was unobtainable from this 60-year-old man (fig. 5). He was first seen with marked bilateral chemosis, proptosis, periorbital edema and generalized reduction in ocular motility. Clinical and laboratory evidence for thyrotoxicosis was negative. The exact duration of his disease was unknown. He had developed a corneal ulcer with perforation, O.S. Immediate bilateral orbital decompressions were done, and the postoperative appearance is illustrated in Figure 5. In spite of this, the marked orbital congestion persisted. He was placed on diuretics and given condensation shields with little change in his clinical condition. Pituitary radiation was then begun, and he was given a total dose of 4,000 r. Improvement

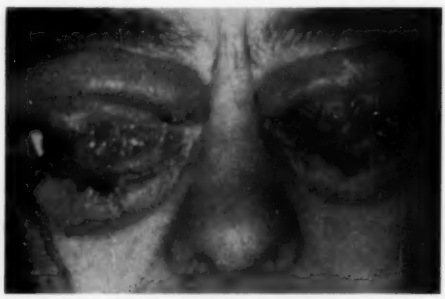


Fig. 5 (Schultz, Hamilton and Braley). A 60-year-old man without evidence of thyrotoxicosis following orbital decompressions for endocrine exophthalmos.

began to occur approximately four weeks after radiation was begun and he has gradually improved to the present time.

Discussion

The incidence of ocular signs and symptoms in Graves' disease will be encountered in approximately 75 percent of patients with this disorder. Approximately one third of these patients will have symptoms of definite clinical significance and about 10 percent will have serious eye complications. Control of thyrotoxicosis can be expected to alleviate the ocular signs and symptoms in 90 percent of patients and improvement may occur in many of the remainder. A small percentage of patients will develop more serious ocular complications after I^{131} but we discovered no means of predicting which patients will be so affected.

Ophthalmoplegia in this group of patients was the most significant residual disability encountered. Periorbital swelling is usually significantly reduced with control of thyrotoxicosis and further reduction frequently occurs with time alone.

Proptosis either is unaffected or increased after the use of I^{131} and even in cases where increases are considerable, the patient is frequently without complaints. This finding suggests that too much emphasis has been placed on the proptotic component of the endocrine eye lesion as an index of the severity of the eye disorder. Although corneal ulcerations and isolated instances of optic nerve damage can occur, in relation to proptosis, these complications are extremely rare in thyrotoxic patients treated with I^{131}. Likewise, permanent objective changes in visual function were rare in thyrotoxicosis but transient reduction in central acuity was a common subjective complaint.

Lid retraction was observed to persist in some cases long after control of thyrotoxicosis, suggesting that it is not a direct result of toxicity. The components of the endocrine eye lesion, which have been discussed, can occur singly or in any combination and with all degrees of severity. They can be present both in patients with and without thyrotoxicosis. It seems unreasonable, therefore, to classify any patient with exophthalmos as being a pure thyroid or pure pituitary type, and it is unlikely that a single cause will be found for any of these components.

The disappearance of ophthalmoplegia in 50 percent of thyrotoxic patients who are treated with I^{131} suggests that the hyperfunctioning thyroid gland plays a direct role in this component of the eye lesion. Ophthalmoplegia has in many previous reports been considered a feature of the "pituitary type" of exophthalmos. It is interesting that a significant percentage of patients with ophthalmoplegia have associated skeletal myopathy.

The presence of pretibial myxedema in thyrotoxicosis, while rare, nevertheless suggests that such a patient is more likely to have serious ocular complications which will be less likely to respond to I^{131}.

Patients without thyrotoxicosis who present a clinical picture similar to the endocrine eye lesion frequently have predominately unilateral disease and a high incidence of ophthalmoplegia. While this may imply that pituitary dysfunction is playing a dominant role, these patients will frequently show a positive Werner's test. Even without evidence of thyrotoxicosis, endocrine dysfunction should be suspected in cases of unilateral proptosis with ophthalmoplegia. This consideration may in some instances save extensive and unnecessary neurosurgical explorations.

Detailed management of the endocrine eye lesion must be individualized. There are, however, some general procedures which we have followed in treatment of patients suspected of endocrine eye disease. I^{131} uptakes, protein-bound iodine, basal metabolism rate and serum cholesterol values are obtained along with orbital and skull X rays in many cases. Examination is done by both an ophthalmologist and an internist. The pa-

tient is carefully examined for evidence of corneal changes, field loss, increase in intraocular pressure, and muscle paresis, and for clinical evidence of hyperthyroidism.

If the patient has thyrotoxicosis, we believe the first and most important step in the management of the eye lesion is to control the hypermetabolism with I^{131}. This approach is also used in other centers.[7] If the laboratory values do not support a diagnosis of thyrotoxicosis, the patient is given tri-iodothyronine for five to 10 days and repeat I^{131}-uptake studies are obtained. Failure of physiologic suppression of the I^{131} uptake is regarded as evidence of endocrine dysfunction. Frequently such patients will show clinical signs of hypermetabolism. Such patients may show improvement of the eye lesion following a therapeutic dose of I^{131}. In several of these cases, however, we have continued the tri-iodothyronine for a period of several weeks. The rationale being that normal pituitary suppression is lacking and that tri-iodothyronine may help. In such patients we have observed some improvement, but the number of cases is too small and the response too inconsistent to permit analysis. Likewise, in some instances we have prescribed tri-iodothyronine for patients who have only proptosis and a positive Werner's test but who lack clinical signs of hyperthyroidism. Regression of proptosis has been observed in some of these cases.

In the acute congestive forms of the endocrine eye lesion, or in those rare cases where proptosis and chemosis progress to the extent that corneal damage occurs or is impending, we have resorted to pituitary radiation. The dose being in the range of 4,000 to 5,000 r. This has been employed in all but one case to patients in the nontoxic group. Progression of the disease has been halted in almost all instances but sudden improvement or return to normal has not been noted. Supportive therapy may be of considerable help in this severe group. This consists of the use of diuretics, elevation of the head at night, lid adhesions, and wearing of condensation shields over the eyes, as well as assuring attainment of a euthyroid state. If gradual improvement with conservative measures is not observed, we will then consider pituitary radiation.

Summary

1. This paper reports the incidence of ocular signs and symptoms in 165 patients with thyrotoxicosis and emphasizes that clinically similar findings can occur in patients without laboratory evidence of hypermetabolism.

2. The aggregate of ocular complications observed has been called the endocrine eye lesion and consists of four basic components: (a) proptosis, (b) ophthalmoplegia, (c) periorbital swelling, (d) lid retraction.

3. The amount of proptosis is not a reliable index of the severity of the eye disease and frequently may represent the more asymptomatic component.

4. The ocular symptoms most commonly noted are burning, scratching, tearing, diplopia, and transient changes in visual acuity. These symptoms appear to be related primarily to components other than proptosis.

5. Of the 165 patients with thyrotoxicosis who were treated with I^{131}, 120 originally had one or more components of the endocrine eye lesion and were symptomatic. The eye lesion was clinically judged to be moderate to severe in about one half of the patients affected.

6. After control of thyroid function ocular symptoms were improved or eliminated in 90 percent of patients. This alleviation of symptoms correlated in time with reduction in eye signs other than proptosis. Proptosis increased 1.5 mm. or more in 50 percent and remained the same in approximately 40 percent of the patients.

7. The average exophthalmometric reading in toxic patients with eye signs was 17.5 mm. compared to 14.7 mm. in toxic patients without ocular complications. The maximum increase in proptosis was 8.0 mm. However,

the maximum difference between O.D and O.S at any one time did not exceed 2.5 mm. in patients with thyrotoxicosis.

8. The sex incidence of thyrotoxicosis was observed to be five females to one male. However, the percentage of men and women who developed the eye lesion was nearly the same (71.6 percent and 71.5 percent respectively).

9. Lid retraction may persist after control of thyrotoxicosis.

10. Gross ophthalmoplegia was observed in 14 percent of all the thyrotoxic patients and complete recovery of muscle function was observed in 50 percent when thyrotoxicosis was controlled.

11. Patients who displayed skeletal myopathy had a higher incidence of eye signs and a much higher incidence of ophthalmoplegia. These patients also showed poor recovery after control of toxicity.

12. All patients with pretibial myxedema showed eye signs which were usually severe and responded poorly to treatment.

13. A small group of nonthyrotoxic patients presenting clinically similar eye findings is reported. These patients showed: (a) A high percentage of unilateral disease, whereas the thyrotoxic patient almost always has bilateral involvement. Differences in exophthalmometric readings between O.D and O.S. were as much as 8.0 mm. (b) Ophthalmoplegia was a frequent complication. (c) A positive Werner's test suggesting endocrine dysfunction was found in 87.5 percent.

14. A brief outline of clinical management of the endocrine eye lesion is presented.

University Hospitals.

Since this paper was submitted, it has come to the authors' attention that similar observations have been reported by R. M. Day, Tr. Am. Ophth. Soc., **57**:572, 1959, which are also in agreement with results reported by H. E. Hamilton, E. L. DeGowin, and R. O. Schultz, J. Lab. & Clin. Med., **52**:817 (Nov.) 1958.

REFERENCES

1. Mulvaney, J. H.: Am. J. Ophth., **27**:589, 1944.
2. Hamilton, H. E., Schultz, R. O., and DeGowin, E. L.: A.M.A. Arch. Int. Med., **105**:675 (May) 1960.
3. Brain, W. R.: Lancet, January 17, 1959, p. 109.
4. Schultz, R. O., Van Allen, W. M., and Blodi, F. C.: A.M.A. Arch. Ophth., **63**:217, 1960.
5. Curtis, A. C., Cawley, E. P., and Johnwick, E. B.: Arch. Dermat. & Syph., **60**:318, 1949.
6. Werner, S. C.: Am. J. Med., **18**:608-612, 1955.
7. Henderson, J. W.: J. Michigan M. Soc., **56**:849-853, 1957.

COLISTIN IN PSEUDOMONAS INFECTION*

REPORT OF A SUCCESSFULLY TREATED CASE

DAN M. GORDON, M.D., AND JOHN M. MCLEAN, M.D.
New York

Pseudomonas (pyocyaneous) aeruginosa is probably the most feared of all ocular infectious agents. Any drug which offers hope of successfully combating this dread organism is a welcome addition to our antimicrobial armamentarium. For this reason, we are reporting a single case of pyocyaneous infection successfully treated with colistin (Colymycin®) in the hope of stimulating further studies in human beings with this antibiotic.

Colistin is a new antibiotic isolated from the micro-organism Aerobacillus colistinus. It is effective against a wide range of gram-negative organisms and moderately so against some gram-positive ones. The antimicrobial spectrum includes Salmonella, Escherichia, Pseudomonas, Brucella, Shigella,

* From the New York Hospital—Cornell University Medical Center. Colistin is the generic name of the antibiotic Colymycin® (American) and Colimycin (Japanese).

Hemophilea, Spirillea, Micrococci, and Proteus. Aqueous solutions are stable within the range of pH 2.0 to 10, though the acid region is preferable.

In June, 1958, Henry Allen told one of us (D. M. G.) that three cases of ocular Pseudomonas infection had been successfully treated with the Japanese antibiotic, Colimycin, at Massachusetts Eye and Ear Hospital. Following this conversation, attempts were made to obtain a supply of this drug, and eventually some was received from Japan through the courtesy of Dr. S. Noyori. Later an opportunity arose to try Colimycin on a proved case of Pseudomonas infection which had not been treated previously with any other antimicrobial. It is our understanding that, while the three successes referred to had undoubtedly been effected by Colimycin, the issue had been clouded somewhat by previous use of other antimicrobials.

Case report

Only the relevant details will be given in the following case report:

Mr. A. C., aged 72 years, had had several attacks of dendritic keratitis in his left eye since 1910, leaving his cornea badly scarred. There had been a concomitant severe uveitis. On December 6, 1958, he had a successful, uncomplicated partial lamellar keratoplasty (J. M. Mc.) for threatened rupture of a descemetocele. The resultant vision was only hand movements, and anterior and posterior synechias which had been present before operation remained. This transplant had been planned as a structural operation, to be followed later by a penetrating one for visual purposes. Following this, the patient went to Florida, where the eye again began to trouble him.

He was seen on March 7, 1959, by Dr. D. Kasner, who found a bullous keratopathy with no evidence of infection. The patient was placed on topical hydrocortisone and scopolamine with relief of symptoms and paling of the globe. On April 10, 1959, there was another similar attack which was again treated with the same medication. He was seen here on April 13th with ulceration of the graft plus severe uveal reaction. A culture was positive for Pseudomonas aeruginosa.

On April 15, 1959, when he was started on treatment with Colimycin, the picture was one of a malignant corneal ulcer with a massive hypopyon. There was no light perception. There was no history of trauma. It is postulated that one of the bullae had ruptured and become contaminated.

He was given a topical solution of 500,000 units of Colimycin dissolved in 7.5 cc. of sterile water to use as eyedrops as often as possible at home. This meant several times an hour the first several days. The patient was given an intramuscular injection of 500,000 units of Colimycin. This was repeated two days later. Recent† information indicates that these two single intramuscular injections were unlikely to achieve sufficiently high blood and tissue levels to affect the inflammatory process.

When the patient was seen on the third day, there was definite improvement which continued throughout the course of therapy. On the fifth day he stated that he had had severe pain the preceding two days. His eye was pale but the tactile tension was "mushy." Two days later (April 22nd) the tactile tension was recorded as "normal to touch," and the vision was "light perception and projection with questionable recognition of hand movements." At this time the concentration of the Colimycin eyedrops was decreased to 500,000 units in 15 cc. of water.

Colimycin therapy was discontinued on May 7, 1959. At that time vision was recorded as "hand movements." The graft was edematous but not bullous, preventing examination of the fundus. The peripheral surrounding cornea was clear with an old iris adhesion to the endothelial surface. The result is an amazing one as attested by the photographs of this case (figs. 1–4), especially since the chief reliance was upon topical therapy.

Summary and Discussion

A case of Pseudomonas infection of the cornea with accompanying hypopyon successfully treated with colimycin is reported in the interest of publicizing the availability of this drug for clinical trial in ocular Pseudomonas infection. The last previous case of intraocular infection seen by one of us (D. M. G.) resulted in enucleation despite intensive parenteral, topical, and intraocular polymixin B therapy.

In retrospect we feel that subconjunctival injections of colimycin (50,000 to 100,000 units in water) might have been attempted, although it is doubtful if this would have been more successful. In intraocular infection following surgery, this should certainly be utilized along with irrigation of the anterior chamber with a solution of approximately 100,000 units per cc.

441 East 68th Street (21).
525 East 68th Street (21).

Footnote

Emergency supplies of colistin (Colymycin®) can be obtained from Dr. John J. Pepper of Warner-Lambert Research Laboratories, Morris Plains, New Jersey.

† Personal communication, Dr. John J. Pepper.

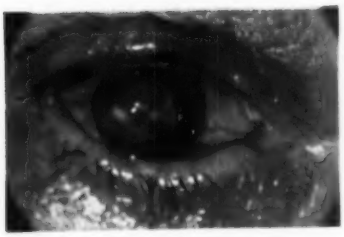


Fig. 1

Fig. 2

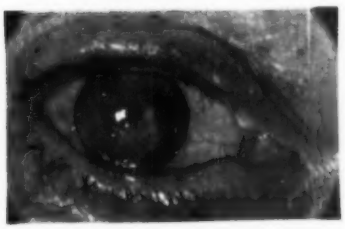


Fig. 3

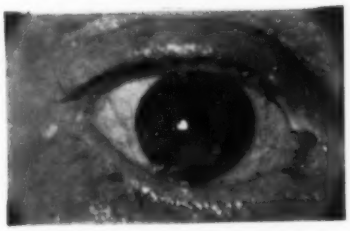


Fig. 4

Figs. 1-4 (Gordon and McLean). Colimycin in Pseudomonas infection.

Fig. 1. Day of initial treatment.
Fig. 2. Twelfth day of Colimycin.
Fig. 3. One week after cessation Colimycin.
Fig. 4. Two weeks after cessation Colimycin.

BIOPSY OF THE TRABECULAR MESHWORK*

In 50 cases of chronic primary glaucoma

H.-H. Unger, M.D., and J. Rohen, M.D.
Freiburg im Breisgau, Germany

Tissue disks obtained by Elliot's trephining operation may be used as a biopsy material (Unger, 1956, 1957). By this method we examined the trabecular meshwork of more than 50 glaucomatous eyes.

With this paper we continue our studies on the morphology and pathology of the trabecular meshwork in the human eye (Rohen and Unger), and on the structure of the inner wall of Schlemm's canal (Unger and Rohen). Fundamental results about the cause of increased resistance to aqueous outflow are still lacking.

We have recently demonstrated that, in cases of absolute glaucoma,† there are two places within the meshwork where morphologic alterations may originate:

1. On the ground substances (glass membrane) enveloping the central core of the trabecular beams (enormous thickening of these substances, loss of the usual staining affinity, decrease of reactivity to peroidate, and so forth).

2. On the inner wall of Schlemm's canal (alterations of a degenerative nature, circumscript cellular proliferations).

Biopsy material now gives us the opportunity to examine early and less progressive glaucomas in tissues which are unchanged by autolysis. We used the same methods for histologic preparation as described in our previous papers. From 150 to 200 sections of each Elliot trephination (corneoscleral disk) were examined, a total of over 10,000 sections. Table 1 shows the clinical data and the histologic findings.

So far we have obtained Elliot's trephinations from 140 eyes; 58 disks contained a small part of Schlemm's canal and the adjacent meshwork; 82 showed only Descemet's membrane and the top of the trabeculae joining the deep corneal lamellae. The latter were unfit for our investigations.

Our report refers to 50 patients (24 eyes with chronic congestive glaucoma, 34 eyes with simple glaucoma; eight patients have had operations on both eyes).

Out of 20 patients with *chronic congestive glaucoma* only 10 had glaucomatous atrophy but these 10 were not quite identical with those who had an altered meshwork. Seven had an extensive loss of visual functions. The average age was less than in the cases with simple glaucoma.

In contrast to that, 21 out of 34 eyes with *simple glaucoma* showed glaucomatous atrophy but 25 eyes had an acuity which was better than 5/10. In only one case were heavy histologic alterations combined with nearly normal clinical data. On the other hand, two eyes with progressive glaucoma had an unchanged inner wall of Schlemm's canal and unchanged trabeculae within the trephined region of the filtration angle. Of all those with simple glaucoma only six patients (44, 51, 56, 64, 78 and 81 years of age) had an unaltered meshwork.

We got the impression that our biopsy results may be divided into different phases but we can only give some descriptive examples drawn from our research. Each example represents a group of exactly the same or nearly similar alterations:

1. *Thickening of the trabecular glass membranes* with or without intertrabecular

* From the Department of Ophthalmology, University of Freiburg im Breisgau, Director: Prof. Dr. W. Wegner, and the Institute of Anatomy, University of Mainz, Director: Prof. Dr. A. Dabelow.

† Rohen, J., and Unger, H.-H.: Zur Morphologie und Pathologie der Kammerbucht des Auges. Verl. d. Akad. d. Wissensch. u. d. Lit., Mainz, Verlag Franz Steiner, Wiesbaden, 1959.

TABLE 1

CLINICAL DATA AND HISTOLOGIC FINDINGS

Case Number	Name	Sex	Age	Eye	Refraction	Acuity	Cupping of Optic Nerve	Atrophy of Optic Nerve	Loss of Visual* Field	Glass Membrane Thickened	Inner Wall of Schl. Canal Thickened	Cellular Proliferation	Hyalinization, Disintegration of Meshwork
						a. CHRONIC CONGESTIVE GLAUCOMA							
93	O.H.	♂	48	r	E	5/3							
8	A.K.	♀	39	l	E	5/4p					+		
34	L.B.	♀	54	r	H	5/5							
40	O.R.	♂	58	l	E	5/5							
98	W.K.	♂	62	l	H	5/4p			+				
89	E.G.	♀	61	r	H	5/5p	+				+	+	
13	K.T.	♂	72	r	M	5/7p	+			+	+	+	
137	A.L.	♀	63	l	H	5/4	+		+				
50	J.O.	♀	71	r	H	5/5	+		+		+		
83	F.K.	♂	76	r	M	5/7p	+		+	+			
55	H.K.	♀	41	l	E	5/4p	+	+	++				
58	H.K.	♀	41	r	E	5/4	+	+	++				
54	M.T.	♀	65	l	E	5/5p	+		+				
62	M.T.	♀	65	r	E	5/5	+	+	++				
107	T.S.	♀	46	l	E	5/5	+	+	++	+	+	+	
59	M.B.	♀	53	r	E	5/7p	+	+	++				
27	W.S.	♂	59	r	M	5/10	+	+	++				
30	W.S.	♂	59	l	E	5/3p	+						
91	E.F.	♂	43	l	E	5/15	+	+	++	+	+	+	
123	J.K.	♂	55	l	M	5/15	+	+	++	+	+	+	
136	J.K.	♂	55	r	M	5/4	+		+				
68	A.N.	♀	52	l	E	5/20	+	+	+++				
108	M.M.	♀	47	r	E	5/50	+	+	+++	+			
94	A.Z.	♀	60	r	E	1/50	+	+	+++	+			
						b. SIMPLE GLAUCOMA							
10	E.M.	♀	44	r	E	5/4							
32	E.M.	♀	44	l	E	5/5							
135	S.G.	♀	69	r	H	5/4				+	+	+	
28	K.S.	♀	64	l	M	5/5p	+						
47	M.B.	♀	56	l	M	5/5p	+						
129	H.R.	♀	55	l	M	5/4	+		+	+	+	+	
7	B.H.	♀	61	r	H	5/4p	+		+	+			
38	K.L.	♂	51	l	E	5/4p	+		+				
87	M.S.	♀	69	r	E	5/5	+		+	+			
126	E.S.	♀	63	r	H	5/5p	+		++	+	+	+	
81	F.S.	♀	51	r	E	5/4p	+	+	+	+	+		
128	L.W.	♀	59	r	H	5/4p	+	+	+	+	+		
106	A.R.	♀	64	r	E	5/7p	+	+	+	+			
104	M.R.	♀	57	r	H	5/4	+	+	++	+	+		
118	E.K.	♂	47	l	E	5/4p	+	+	++		+	+	
17	B.S.	♀	59	r	H	5/5p	+	+	++	+	+		
105	E.A.	♀	72	l	E	5/5p	+	+	++	+	+		
141	E.A.	♀	72	r	E	5/5	+		+	+	+		
121	E.M.	♂	54	l	M	5/5p	+	+	++		+	+	
9	E.M.	♂	64	l	H	5/7	+	+	++		+	+	
36	H.G.	♀	79	l	M	5/7	+	+	++	+			
44	H.G.	♀	79	r	M	5/7	+	+	++	+			
127	F.S.	♂	68	r	M	5/7	+	+	++	+	+		+
113	L.K.	♂	69	l	M	5/7p	+	+	++	+	+		
66	L.L.	♀	61	r	H	5/10p	+	+	++	+			
120	F.S.	♂	68	l	M	5/10p	+	+	++	+	+	+	
122	J.T.	♂	70	r	H	5/15	+	+	++	+	+	+	
124	S.H.	♀	77	r	M	5/15	+	+	++	+	+	+	
116	M.K.	♀	73	l	E	5/7	+			+	+		
117	M.K.	♀	73	r	E	5/20	+		++	+	+		
101	K.B.	♀	81	r	E	3/50	+	+	++				
2	O.S.	♂	78	l	M	1/20	+	+	++				
84	F.O.	♀	70	r	E	1/50	+	+	++	+	+	+	
102	A.V.	♂	76	l	?	FC.	+	+	+++	+			

+ = blind spot enlarged, Bjerrum skotoma; small narrowing of nasal field.
++ = loss of nasal field; Bjerrum scotoma; center spared.
+++ = extensive field loss.

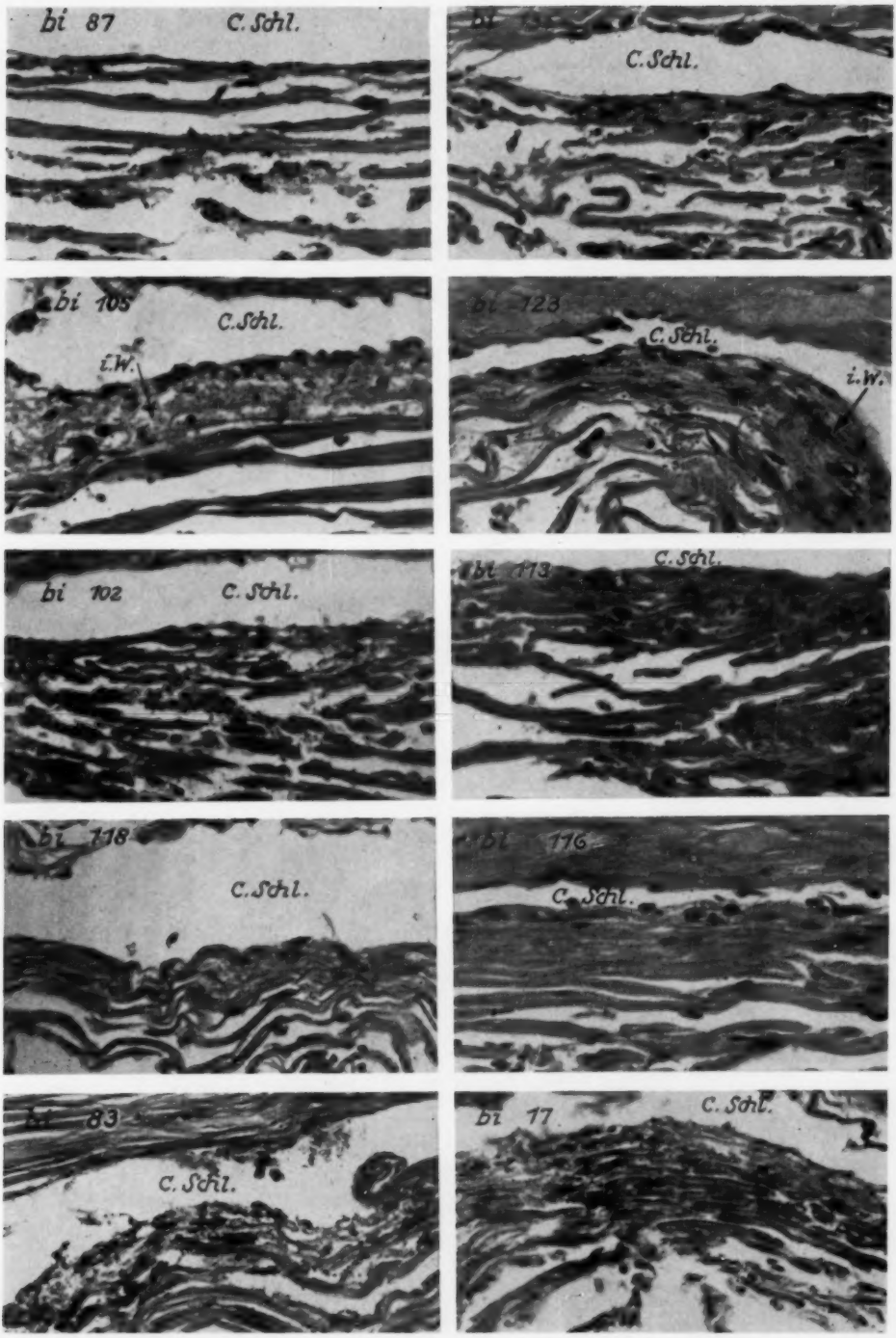


Fig. 1 (Unger and Rohen). Medium-power view of 10 selected sections through Elliot trephinations, showing different phases of glass-membrane changes with or without intertrabecular adhesions. (Stieve, hematoxylin-eosin.)

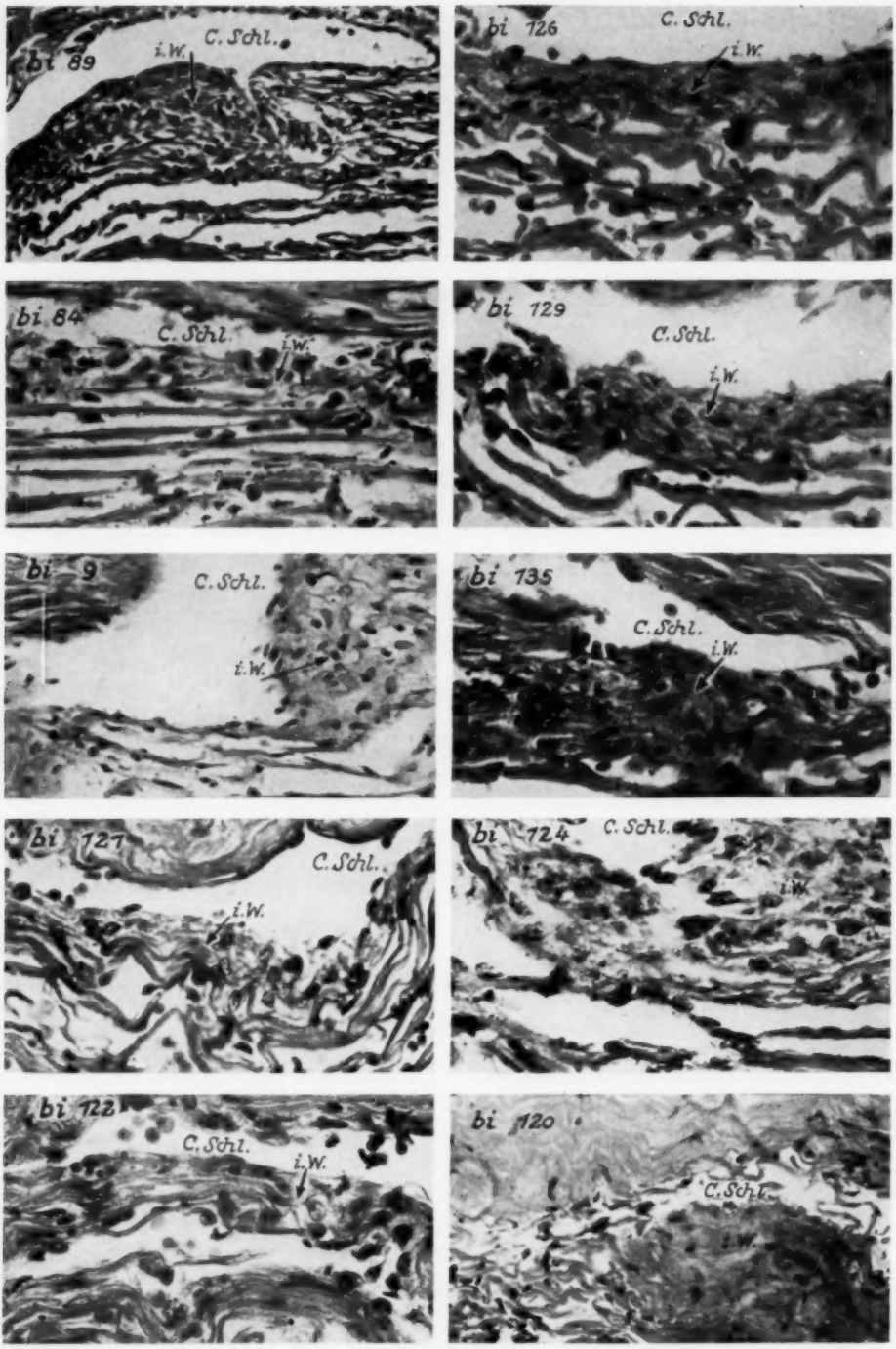


Fig. 2 (Unger and Rohen). Medium-power view of 10 selected sections through Elliot trephinations, showing changes at the inner wall of Schlemm's canal. Slight multiplication of endothelial cells, excessive tumorlike proliferation and degenerated tissue in compact form. (Stieve, hematoxylin-eosin.)

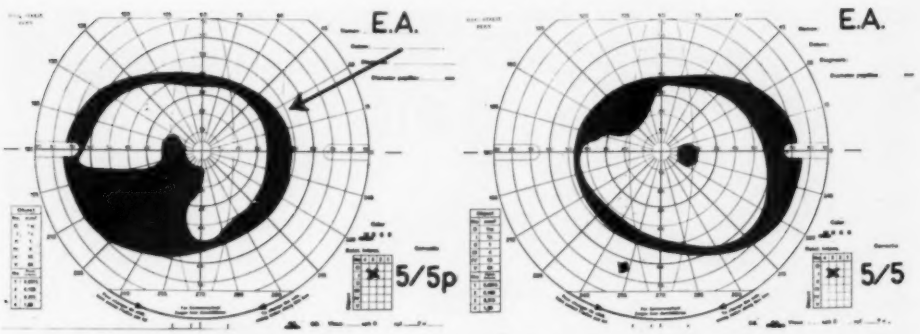


Fig. 3A (Unger and Rohen). Visual fields in Case 105, E. A., ♀, aged 72 years, simple glaucoma.

adhesions and conglutination of lamellae. If synechias have set in, they are first seen in the vicinity of Schlemm's canal. Then the outermost interstices are narrowed or obstructed (figs. 1, 3B, and 3C).

2. *Circumscript proliferations* of endothelial cells in the inner wall area of the canal of Schlemm (fig. 2). At least two types of cells can be noted there:

a. Cells with plump, pale nuclei which appear to be enlarged. These cells are to be found more often with proliferative alterations of the inner wall of Schlemm's canal.

b. Cells with dark nuclei of various shapes.

There were four disks from Elliot trephinings in our material with excessive circumscript proliferations (figs. 4B and 4C).

3. *Gradual disintegration, hyalinization and loss* of the meshwork's normal architecture, especially in old proliferative zones. Most of the trabeculae are replaced by homogeneous tissues sparse in nuclei (fig. 2, biopsy 120). These changes are well known to

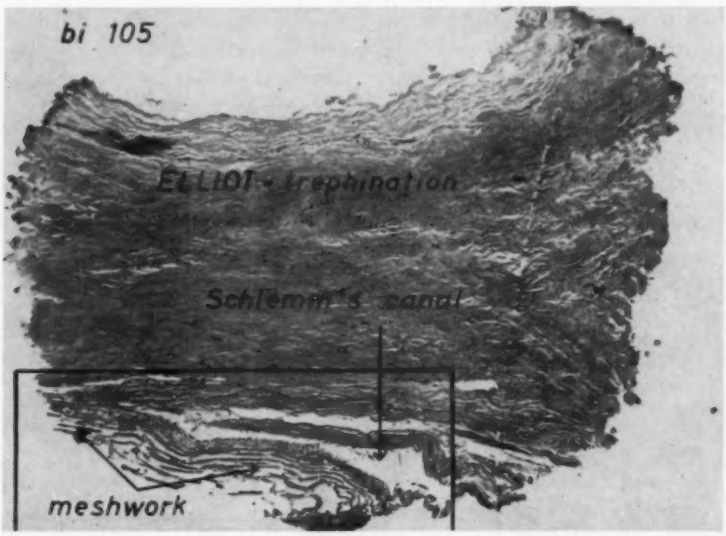


Fig. 3B (Unger and Rohen). Case 105. Sagittal section of Elliot disk (left eye).

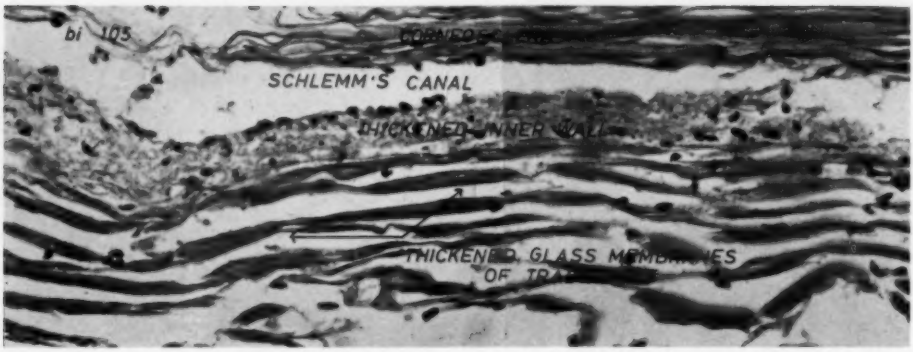


Fig. 3C (Unger and Rohen). Case 105. High-power view of trabeculae, showing swelling of the glass membrane. The trabecular spaces are in good condition. There is a striking circumscript thickening and a foamy appearance of the inner wall area of Schlemm's canal. (Figures 3B and 3C, Stieve, hematoxylin-eosin.)

us from previous study of absolute glaucoma.

This succession of findings (1-3) does not attempt to classify the pathologic phases. It is possible that disintegration precedes proliferation and vice versa. This paper is considered to be a preliminary report.

It is impossible to state definite correlation between histologic and clinical findings on only 50 cases of glaucoma but when we consider the evidence in Table 1, it appears that pathologic changes of the meshwork occur more frequently with simple glaucomas than with congestive types and more frequently with older glaucomas than in the early stages. To a much lesser degree, these trabecular findings can be present in normal eyes of individuals of advanced age (Rohen and Unger).

Histologic examinations of the chamber angle of glaucomatous eyes have been made by many authors. They investigated enucleated eyes with absolute glaucoma or tissues from post-mortem material. In a previous paper (Rohen and Unger), we have discussed the findings of Tartuferi, Sarti, Polya, de Vries, Henderson, Greeves, Rones, Duke-Elder, Reese, Teng, Paton and Katzin, Theobald and Kirk, François, Rabaey and Neetens, et al. In the meantime new results which refer to this subject have been reported by Kornzweig, Rohen and Unger, Kornzweig, Feldstein, and Schneider, Teng, Katzin, and Chi, Flocks, Kurus, et al. We

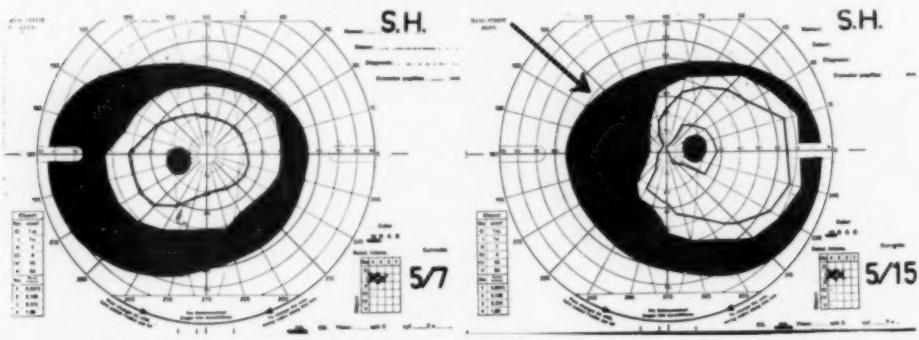


Fig. 4A (Unger and Rohen). Visual fields in Case 124, S. H., ♀, aged 77 years, simple glaucoma.

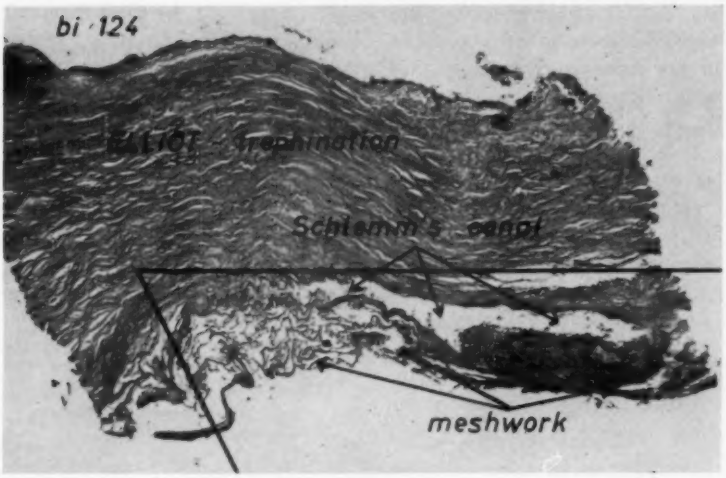


Fig. 4B (Unger and Rohen). Case 124. Sagittal section of Elliot disk (right eye).

think that our findings in a certain degree are similar to those of Flocks (one case of early glaucoma), Kornzweig, et al. (seven cases of early glaucoma), as well as the very important findings of Teng et al. (four cases of early glaucoma) as far as we can compare with the excellent figures given in his last paper. We think it is too early to speak about histologic findings of the meshwork as etiologic factors of glaucoma. Further careful studies must be made.

It is most probable that within the meshwork, the main impediment to aqueous outflow is represented by the inner wall of Schlemm's canal. Therefore, we have a special interest in the pathology of this region.

We agree with Vail that the pathologic findings of the trabecular meshwork in cases

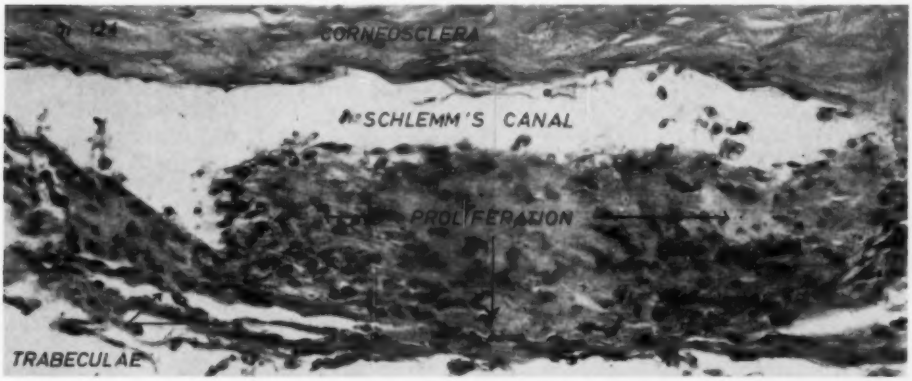


Fig. 4C (Unger and Rohen). Case 124. High-power view of Schlemm's canal. Trabecular glass membranes are slightly thickened. There is a tumorlike proliferation of endothelium in the region of the inner wall. (Figures 4B and 4C, Stieve, hematoxylin-eosin.)

of simple glaucoma are of a degenerative nature. They may contribute to the increase of resistance to the aqueous circulation, thus making glaucoma worse.

Conclusion

Fifty-eight corneoscleral disks of Elliot trephinings (from 50 patients) have been examined for histologic alterations of the trabecular meshwork with early and less progressive glaucoma (chronical congestive glaucoma: 24 eyes; simple glaucoma: 34 eyes).

Especially in progressive cases of simple glaucoma two types of biopsy alterations can be observed:

1. Changes of the glass membrane of the trabeculae, with or without intertrabecular adhesions.

2. Changes of the inner wall of Schlemm's canal with or without circumscript proliferation of endothelial cells.

Four cases showed an excessive, tumor-like increase in the number of cells. In one case the meshwork was replaced by amorphous tissues.

These alterations are of a degenerative nature. It is probable that they contribute to the obliteration of the intertrabecular aqueous passages.

Schumannstrasse 14.

References

Duke-Elder, S.: Textbook of Ophthalmology. St. Louis, Mosby, 1941, v. 3, p. 3341.
Flocks, M.: Tr. Am. Acad. Ophth., 1958, p. 556.
François, J., Rabaey, M., and Neetens, A.: Arch. Ophth., **55**:488, 1956.
Garron, L. K., Fenney, M. L., Hogan, M. J., and McEwen, W. K.: Am. J. Ophth., **46**:27, 1958.
Greeves, R. A.: Proc. Roy. Soc. Med. London, Sect. Ophth., **7**:112, 1913-14.
Henderson, T.: Ophth. Rec., **17**:534, 1908.
———: Glaucoma, London, Arnold, 1910, pp. 34-38.
Kornzweig, A. L.: Ophth. ibero-am., **18**:12, 1956.
Kornzweig, A. L., Feldstein, M., and Schneider, J.: Am. J. Ophth., **46**:311, 1958.
Kurus, E.: Klin. Monatsbl. f. Augenh., **132**:201, 1958.
Polya: Ungar. Beitr. **2**:319, 1899.
Reese, A. B.: Am. J. Ophth., **27**:1193, 1944.
Rohen, J., and Unger, H.-H.: Am. J. Ophth., **46**:802, 1958.
———: Zur Morphologie und Pathologie der Kammerbucht des Auges. Mainz, Verl. Akad. Wiss. Lit., Wiesbaden, Franz Steiner, 1959.
Rones, B.: Am. J. Ophth., **21**:239, 1938; **45**:189, 1958.
Sarti, V.: Boll. sc. med. Bologna, **4**:147, 1893.
Tartuferi, F.: Giorn. Acad. med. Torino, **30**:624, 1882.
Teng, C. C., Paton, R. T., and Katzin, H. M.: Am. J. Ophth., **40**:619, 1955.
Teng, C. C., Katzin, H. M., and Chi, H. H.: Am. J. Ophth., **43**:193, 1957.
Theobald, G., and Kirk, H. Q.: Am. J. Ophth., **41**:11, 1956.
Unger, H.-H.: D. O. G. Heidelberg, 1956, München, Bergmann, 1957, p. 59.
———: Arch. Ophth., **158**:509, 1957.
Unger, H.-H., and Rohen, J.: Am. J. Ophth., **48**:204, 1959.
Vail, D.: Year-Book of Ophthalmology, Chicago, Year-Book, 1958, p. 288.
de Vries, W. M.: Nederl. Tijdschr. v. Geneesk., **43**:1688, 1907.

IRIDOCORNEOSCLERECTOMY FOR GLAUCOMA*

CONRAD BERENS, M.D., AND ARNOLD S. BREAKEY, M.D.
New York
Glen Cove, New York

Iridocorneosclerectomy, which was first employed over 30 years ago, combines the best features of the LaGrange,[1] Holth,[2] and Elliot[3] operations, and it has seemed desirable to modify the original technique only slightly since it was first described in 1936.[4]

The long-range efficacy of iridocorneosclerectomy in the control of glaucoma as revealed by statistical studies, bears out earlier conclusions concerning glaucoma surgery, which were arrived at after observations of the work of several distinguished ophthalmologists, that is, J. B. Weeks, who always used the Lagrange operation, R. G. Reese, who performed basal iridectomy and massage, and W. E. Wilmer and J. M. Wheeler who preferred the Elliot trephining operation. John Weeks' long-range results seemed to be superior to those of the other three surgeons.

The technique of iridocorneosclerectomy consists of punching out bits of cornea and sclera after splitting the cornea, thus forming a long wound with a serrated edge. A long filtering cicatrix is produced in a high percentage of cases. Since the success or failure of an operative procedure should be based, whenever possible, upon careful studies over a long period of time, a statistical survey of the postoperative results and complications of 573 eyes following iridocorneosclerectomy and observed for from one to 30 years, are evaluated.

INDICATIONS FOR IRIDOCORNEOSCLERECTOMY

1. Chronic simple glaucoma (open-angle) when the anterior chamber is not too shallow and the angle is not too closed.

2. Secondary glaucoma, in which it may be advisable to combine other procedures such as cyclodialysis, cycloelectrolysis[5] or inclusion of one or both pillars of the iris or merely a section of the base of the iris,[6] which is readily accomplished through the long wound.

3. Glaucoma following cataract extraction, usually combined with iris inclusion, although a peripheral iridectomy may suffice if the pupil is blocked by vitreous.

4. Acute angle-closure glaucoma when the eye is relatively free from congestion and especially when it has been possible to lower tension preoperatively but retardation of aqueous outflow is suggested following bilateral simultaneous bulbar compression.[7]

5. Glaucoma associated with developing cataract, when a narrow complete iridectomy is usually indicated.

6. Angle-closure glaucoma in the late stages when synechias are numerous and outflow is severely impaired.

CONTRAINDICATIONS

1. Buphthalmos, and especially when the sclera is thin.

2. Newly formed vessels on the iris, as in rubeosis irides in diabetes.

3. Atrophy of the conjunctiva and Tenon's capsule, although Tenon's capsule may be transplanted in some cases.

PREOPERATIVE PREPARATIONS

1. Attempt to remove or raise resistance to chronic infections.

2. Retrobulbar hyaluronidase and procaine (four percent) and possibly Diamox to lower tension if it is not controlled well by miotics.

TECHNIQUE OF IRIDOCORNEOSCLERECTOMY

1. A straight or slightly curved (concavity toward the cornea) conjunctival incision, 15 mm. in length, is made 10 mm. from the

* From the Department of Ophthalmology, New York University Post-Graduate School of Medicine, and the Department of Research, New York Association for the Blind. Read in part before the Societe Tunisienne d'ophthalmologie, Tunis, North Africa, May, 1959. Aided by a grant from The Ophthalmological Foundation, Inc.

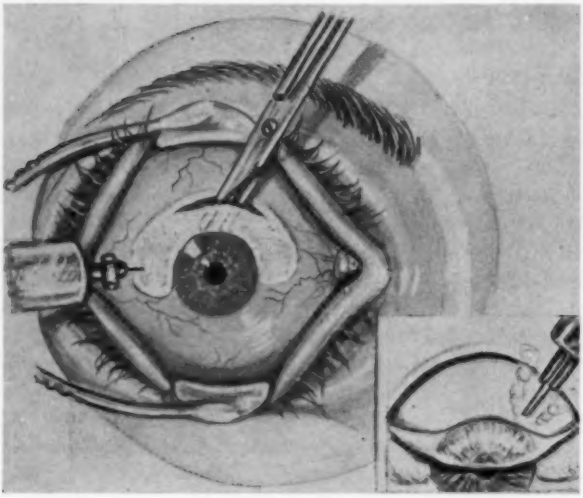


Fig. 1 (Berens and Breakey). A slightly curved or straight conjunctival incision, 15 mm. long is made 10 mm. above the limbus. Procaine and epinephrine solution injected under Tenon's capsule facilitates dissection of a thick flap. (Insert) Bleeding is controlled with the Hildreth cautery and the sclera immediately posterior to the proposed incision is blanched with the cautery.

limbus. The injection of procaine and epinephrine under Tenon's capsule facilitates dissection of the flap.

2. The flap is dissected from the underlying sclera down to the cornea using Stevens scissors, but attempting to avoid cutting the episcleral vessels. The extremities of the incision should not be closer than eight mm. from the limbus (fig. 1). All bleeding should be controlled by means of the Hildreth cautery (fig. 1 insert) and the sclera immediately posterior to the proposed incision should be well blanched with the cautery. We believe that this precautionary measure against hemorrhage may be one reason for the high degree of success of certain glaucoma operations, as noted by Scheie.[8]

3. The conjunctival flap is drawn downward as the cornea is dissected into layers with a special keratome dissector, using a side-to-side movement, extending 1.0 mm. into the cornea (fig. 2). A Tooke corneal splitter (fig. 2-A) or Lungsgaard knife (fig. 2-B) may be used.

If the anterior chamber is moderately shallow, a small narrow cataract knife with a straight back is used. If the anterior chamber is more shallow, a special curved glaucoma knife[9] is safer. This produces a straighter incision on the curved surface of the eyeball (fig. 2-C). In making the incision, the eye is fixed by grasping the sclera below the counterpuncture of the proposed line of incision with special curved forceps[10] or Elschnig forceps. The knife enters the sclera 1.5 mm. from the limbus and is directed slightly downward. When the anterior chamber is entered, the knife is passed horizontally across the anterior chamber and the counterpuncture is made to emerge from the sclera 1.0 mm. from the limbus (fig. 2-C). The knife is repeatedly rotated slightly to allow the aqueous to escape slowly and then the incision is completed, producing a wound 5.0 mm. in length. A scleral flap 1.5 to 2.0 mm. in diameter is made accurately by turning the blade forward as the knife is drawn upward.

If the anterior chamber is extremely shallow, a slanting incision is made into the anterior chamber near the lower limbus with a small Ziegler or narrow cataract knife, previously dipped in methylene blue. A scratch incision is then made with a keratome 1.5 mm. posterior to the limbus, usually centered slightly nasal to the vertical meridian.

4. A hollow-ground angular keratome[11] may be used, as was first practiced, if the chamber is deep. The patient is directed to

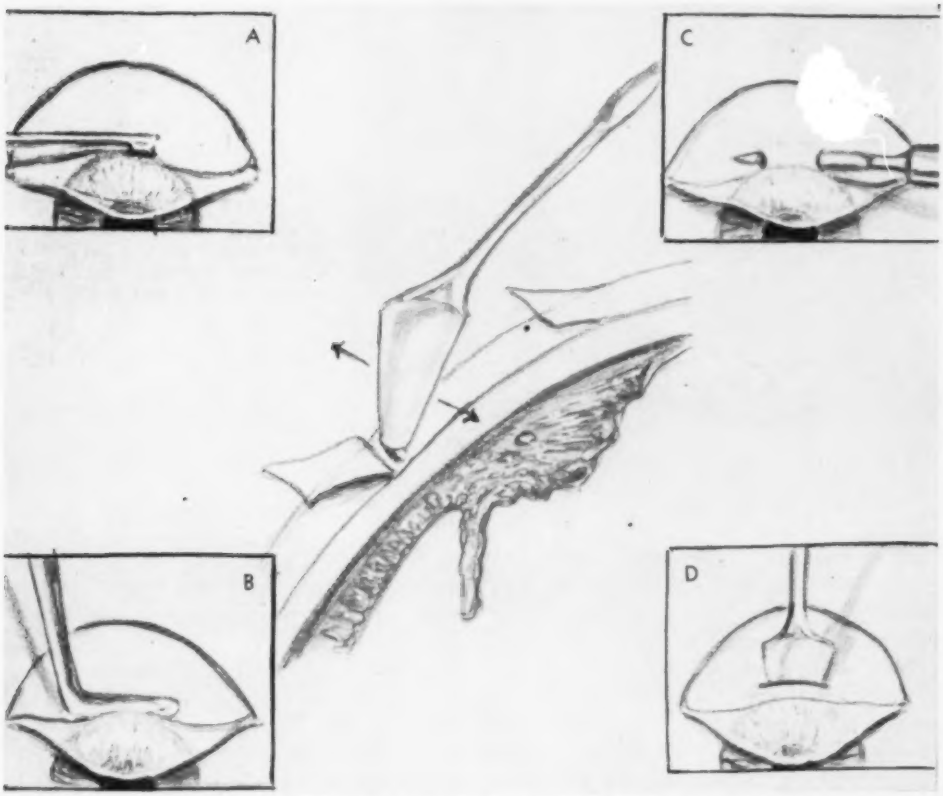


Fig. 2 (Berens and Breakey). The cornea is split to a depth of 1.0 mm. with a keratome dissector. A Tooke corneal splitter (A) or Lunsgaard knife (B) may be used. If the anterior chamber is moderately shallow, a curved narrow glaucoma knife is used in making the scleral section. The blade is passed horizontally across the anterior chamber with a scleral puncture and counterpuncture made 1.5 mm. from the limbus (C). A hollow ground keratome may be used if the anterior chamber is deep (D).

look downward, and the eye is held in this position with fixation forceps applied to the inferior rectus. The incision is made beginning 1.5 mm. above the limbus and extending into the anterior chamber until a wound approximately 5.0 mm. long is obtained (fig. 2-D). Withdrawal of the keratome against one edge of the wound should be made with care, with the tip tilting forward to prevent the iris from prolapsing into the wound, or injury to the lens or cornea.

5. After making the incision with a keratome or glaucoma knife, if prolapse of the iris occurs, an attempt should be made to replace it gently with a spatula by pressing on the iris through the conjunctiva, and by irrigation. If reposition is not accomplished easily, a spatula will exclude the iris from the wound while the scleral punch is being used.

6. The extremities of the scleral wound are extended to the limbus with Stevens scissors, making a narrow opening approximately 5.0 mm. (fig. 3).

7. Corneosclerectomy with a special punch (fig. 4) is performed as follows: While holding the conjunctival flap down with a cotton-wound saline moistened applicator, the sclera

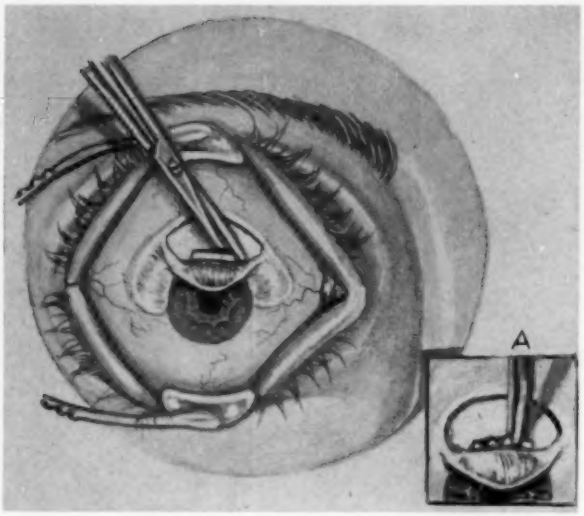


Fig. 3 (Berens and Breakey). Incisions are made toward the cornea at the extremities of the scleral wound. (A) The sclera and cornea are clipped deep within each angle with a special scleral punch, producing a serrated wound.

and cornea are clipped deep within each angle with the Berens scleral punch after passing the lower blade into the anterior chamber. The remaining lip of the scleral flap is clipped away leaving a serrated edge (fig. 3-A). If a punch is not available, the scleral lip of the wound may be grasped with forceps and excised with curved scissors, but this type of incision has a greater tendency to close and does not produce a long filtering wound.

8. PERFORMING THE IRIDECTOMY. The iris is made to prolapse by irrigation or by pressure on the cornea, or is grasped with iris forceps and drawn outward until it may be seized. To avoid injuring the lens, the anterior chamber should not be entered with the forceps. A broad two-cut basal iridectomy is made if a cataract is developing or inflammation is feared, or has been present; otherwise a peripheral iridectomy is performed (fig. 5 insert).

Fig. 4 (Berens and Breakey). Iridocorneosclerectomy punch (Berens).

a. In order to perform a complete iridectomy, after the first radial cut is made, as close to the forceps as possible, with deWecker scissors, the iris is gently torn from the ciliary body by traction forward and toward the uncut side. The second cut is then made (fig. 5), while the base of the blades rest on the corneoscleral wound and the tips of the blades are as close as possible to the forceps.

b. The iris pillars are replaced by irrigating the anterior chamber with Hanks' balanced salt solution while gently stroking the cornea over the pillars. (From tissue culture work by Girard,* the use of normal saline as an irrigation solution is contraindicated. It was found to produce toxic changes on corneal endothelium grown in tissue culture. When injected into the anterior chamber in rabbit's eyes, normal saline produced mild iridocyclitis. Hank's balanced salt solution was found to be less injurious.)

* Personal communication, 1959.

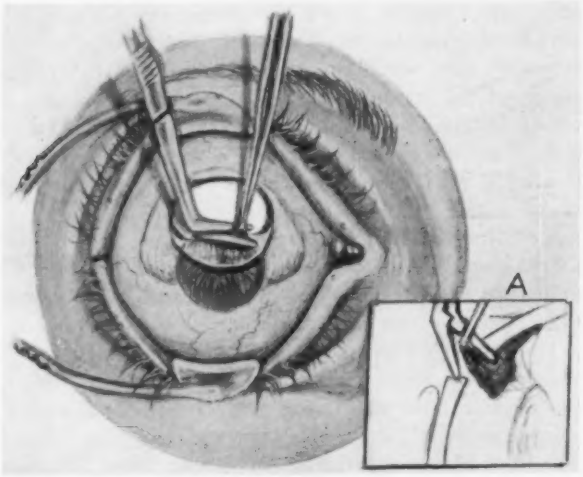


Fig. 5 (Berens and Breakey). A broad, two-cut basal iridectomy is made if a cataract is developing or inflammation is feared or has been present. (A) Peripheral iridectomy is performed unless contraindicated.

c. In secondary glaucoma and glaucoma following cataract extraction, an iris pillar may be incarcerated in one or both angles of the wound. In a few cases, the central part of the iris root has been incarcerated, leaving a round pupil.

9. If the conjunctiva is thin, only a narrow sclerectomy is performed, and a flap of Tenon's capsule is dissected from the area near the superior rectus, partially freed and drawn downward by two double-armed (6-0) black silk sutures. The flap is attached to the episcleral tissue close to the limbus on each side of the wound (fig. 6), and the sutures are passed through the flap and tied externally. This procedure may also be applied to insure a thick flap in other operations where subconjunctival filtration is desired, that is, in trephining, iridencleisis, iridosclerectomy and flap sclerotomies.

10. The conjunctival wound is closed with a running centrally locked double-armed 5-0

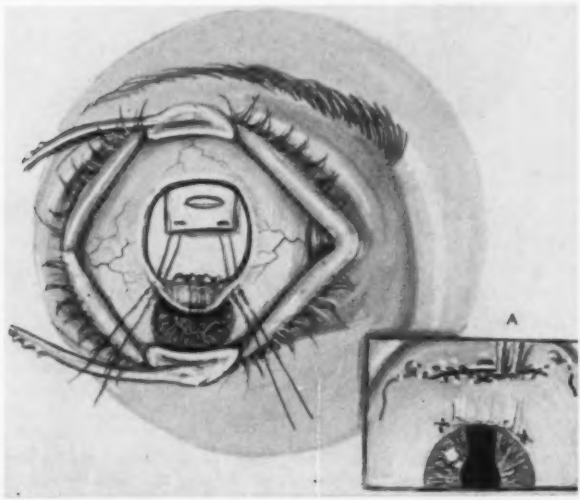


Fig. 6 (Berens and Breakey). If the conjunctiva is atrophic, a narrow sclerectomy is performed and a flap of Tenon's capsule is dissected from the area near the superior rectus, partially freed and drawn downward by two double-armed sutures. The flap is anchored to the episcleral tissue close to the limbus on each side of the wound. (A) The conjunctival wound is closed with a running centrally locked double-armed 5-0 plain catgut suture and the wound edges approximated with forceps except at the extremities.

plain catgut suture. If the conjunctiva is atrophic, silk may be used. The double-armed suture is first introduced and tied in the center of the wound and then the lateral wound is closed with a running stitch. The ends of the suture are locked at the extremities (fig. 6-A). The anchored ends are placed slightly above the highest point of the conjunctival incision in order to draw the conjunctiva upward. After drawing the suture tight, the wound edges are approximated with forceps except at the extremities.

11. A grooved spatula is inserted at one angle of the wound while the anterior chamber irrigator, filled with Hanks' balanced salt solution is inserted in the opposite angle. The blood and fibrin are irrigated from beneath the flap (fig. 7). A minimum amount of the solution is allowed to remain under the flap to balloon it forward and possibly restore the anterior chamber when under pressure of the eyelids. If the anterior chamber is unusually shallow, a blunt 28 gauge hypodermic needle is introduced through the previously made corneal wound near the limbus below, and a small bubble of air is injected [12] (fig. 7A-B). Approximation of the lips of the wound is now completed at the extremities.

Postoperative treatment following iridocorneosclerectomy

The palpebral fissure is filled at the medial canthus with an antiseptic ointment and atropine sulfate (one percent) is placed in the conjunctival cul-de-sac. A light dressing and a Ring's mask are applied with an opening before the sound eye.

The patient is placed in bed with head and torso elevated to 30 degrees and is allowed to be up after 24 hours, routine care being administered.

If in from 24 to 48 hours after operation,

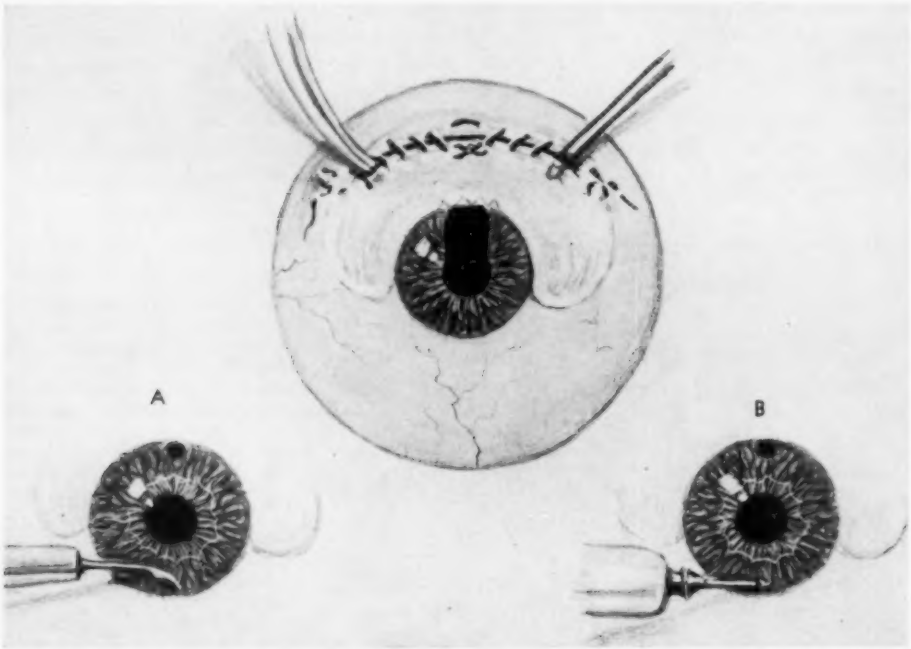


Fig. 7 (Berens and Breakey). A grooved spatula is inserted at one angle of the wound while the anterior chamber irrigator, filled with Hank's balanced salt solution is inserted in the opposite angle. The blood and fibrin are irrigated from beneath the flap. Approximation of the lips of the wound edges is then completed at the extremities. (A) Ziegler knife incision. (B) Injection of air.

TABLE 1

POSTOPERATIVE RESULTS IN 573 EYES FOLLOWING IRIDOCORNEOSCLERECTOMY FOR VARIOUS TYPES OF GLAUCOMA OBSERVED FOR FROM ONE TO 30 YEARS

A. Type of Glaucoma B. Primary Procedure C. Additional Surgery	No. of Eyes	Tension*					Enucleation or Evisceration	Vision†			Visual Fields‡		
		1	2	3	4	5		1	2	3	1	2	3
A. Chronic simple B. 91% C. 14%	436	153 35% 80%	198 45%	49 11%	6 1%	19 5%	11 3%	169 39% 54%	59 13%	197 46%	140 40% 82%	150 42%	65 18%
A. Acute B. 94% C. 16%	78	24 31% 65%	27 34%	9 11%	6 8%	6 8%	6 8%	33 46% 89%	31 43%	8 11%	19 34% 91%	32 57%	5 9%
A. Aphakic B. 95% C. 31.5%	26	4 16% 58%	11 42%	5 19%	1 4%	0	5 19%	7 33% 42%	2 9%	12 58%	1 14% 43%	2 29%	4 57%
A. Secondary uveitis B. 91% C. 33%	28	12 43% 86%	12 43%	2 7%	0	1 3.5%	1 3.5%	18 67% 78%	3 11%	6 22%	9 43% 95%	11 52%	1 5%
A. Absolute B. 25% C. 33%	5	0	2 40%	1 20%	1 20%	0	1 20%	0	4	0	0	0	0
Total: Mean % B. 79% C. 25%	573	193 34% 78%	250 44%	66 11%	14 2%	26 5%	24 4%	227 41% 54%	99 13%	223 46%	169 38% 83%	195 45%	75 17%

* Tension: (1) Controlled (under 25 mm.Hg Schiøtz) without miotics; (2) with miotics; (3) tension reduced (over 25–35 mm. Hg); (4) hypotonic; (5) uncontrolled.
† Vision and ‡ Visual fields: (1) Improved; (2) unchanged ; (3) decreased or lost.

the anterior chamber is restored and the wound is not filtering, gentle massage of the eyeball is started and repeated two to three times daily.

If a silk suture has been used to close the conjunctiva or to anchor Tenon's capsule, it is usually removed on the eighth day.

POSTOPERATIVE RESULTS FOLLOWING IRIDICORNEOSCLERECTOMY*

The postoperative results obtained in 573 eyes observed for from one to 30 years are tabulated in Table 1.

DISCUSSION OF TABLE 1

A total of 573 eyes for various types of glaucoma, observed for from one to 30 years following iridocorneosclerectomy indicates that tension in 34 percent of the eyes was controlled (under 25 mm. Hg Schiøtz) without miotics and 44 percent with miotics for a total of 78 percent of the eyes controlled. Iridocorneosclerectomy was employed as a primary procedure in 79 percent and additional surgery was required in 25 percent of the 573 eyes. Vision was improved or remained unchanged in 54 percent of the series. Of the available 439 visual fields, 73 percent was improved or unchanged following iridocorneosclerectomy.

The results of operation on 436 eyes following iridocorneosclerectomy for chronic simple glaucoma observed for from one to 30 years, revealed that tension in 35 percent of the eyes was controlled without miotics and 45 percent with miotics for a total of 80 percent of the eyes controlled under 25 mm. Hg Schiøtz. Study of 28 eyes with glaucoma secondary to uveitis revealed that in 43 percent, tension was controlled without miotics and 43 percent with miotics for a total of 86 percent of the eyes controlled following iridocorneosclerectomy. The control of tension in 31 percent of 78 eyes affected with acute glaucoma without miotics and in 34 percent with miotics for a total of 65 percent controlled, seems excellent considering the prolonged period of observation of so many

* The compilation of much of these data was made possible through the courtesy of the following ophthalmologists: Drs. S. L. Chamichian, R. M. Sturman, M. Loutfallah, J. W. Overton, B. L. Sheppard, and through the staffs of the New York Eye and Ear Infirmary, the Manhattan Eye and Ear Hospital, the Department of Ophthalmology of the University of Pennsylvania and the authors' private records.

of the patients. The improved or unchanged visual acuity in 89 percent of the eyes, and improved and unchanged visual fields in 91 percent of the eyes, is noteworthy. Only 16 percent of the eyes had secondary operations.

The incidence of enucleation in aphakic eyes (19 percent) seems relatively high. However, in two cases, the eyes were accidently traumatized (one patient injured the eye which had been operated upon when he fell out of bed, and the second was struck in the eye which had been operated upon by a door). In this series of aphakic eyes, tension was controlled with and without miotics in 58 percent; 42 percent had improved or unchanged vision and the visual fields were improved or remained unchanged in 43 percent of the cases in which visual fields were available.

Results in relation to period of postoperative observation

One of the purposes of this study was to learn more concerning the effect of the postoperative time factor on the results obtained following iridocorneosclerectomy. These cases have been divided into three groups as shown in Table 2. In group A, 197 eyes were observed for from one to six years; in group B, 197 eyes were observed for from seven to eleven years, and in group C, 179 eyes were observed for from 12 to 30 years. The majority of the latter group were followed up to 18 years. The number of enucleations increased in the eyes observed for from 12 to 30 years.

Discussion of Table 2

Iridocorneosclerectomy when used as a primary operation for glaucoma, usually controls tension well without further surgery, but, as with other filtering operations, and especially operations which are designed to reduce the secretion of aqueous, the number of additional operations increases with the years, tension is controlled in fewer eyes and visual acuity often gradually deteriorates.

The cases reported in Table 2 include the results of 573 eyes divided into three groups according to the period of postoperative observation following iridocorneosclerectomy. In group A, 197 eyes was observed for from one to six years. Only six percent required additional surgery and tension was controlled in 88 percent of the eyes (with and without miotics). Group B, including patients ob-

TABLE 2

Comparison of results following iridocorneosclerectomy in 573 eyes for types of glaucoma observed for various postoperative periods

Postoperative Period of Observation B. Primary Surgery C. Additional Surgery	No. of Eyes	Tension*					Enuc. or Evis.	Visual Acuity†		
		1	2	3	4	5		1	2	3
Group A 1 to 6 years B. 92% C. 6%	197	91 47% 88%	81 41%	18 9%	0	2 1%	5 2%	91 47% 73%	50 26%	51 27%
Group B 7 to 11 years B. 89% C. 21%	197	72 37% 80%	85 43%	21 11%	5 2%	10 5%	4 2%	84 43% 55%	24 12%	85 45%
Group C 12 to 30 years B. 94% C. 37%	179	30 17% 64%	84 47%	27 16%	9 5%	14 7%	15 8%	52 31% 47%	25 16%	67 53%

* Tension: (1) Controlled (under 25 mm. Hg Schiøtz) without miotics; (2) with miotics; (3) tension reduced (over 25 to 35 mm. Hg); (4) hypotonic; (5) uncontrolled.

† Visual acuity: (1) Improved; (2) unchanged; (3) decreased or lost.

served for from seven to 11 years, shows a gradual reduction in the control of tension (under 25 mm. Hg Schiøtz) in a series of 197 eyes (80 percent controlled with and without miotics), and 21 percent of these eyes required further surgery. In group C, 179 eyes were observed up to 30 years. Tension was controlled in only 64 percent of the eyes, with additional surgery performed in 37 percent of this group. Visual acuity also showed a gradual progressive reduction in the three groups of patients in direct relation to the length of postoperative observation.

Complications following iridocorneosclerectomy

Only a minimum of complications have been observed following iridocorneosclerectomy in 549 retained eyes observed for from one to 30 years postoperatively. These are tabulated in Table 3.

Many surgeons perform iridencleisis because of the good results obtained and the simplicity of the surgical technique. However, in comparing the total results of operations on 597 eyes observed for from one to 18 years following iridencleisis with the results of operation on 573 eyes observed for from one to 30 years following iridocorneosclerectomy, it is evident that the latter procedure controls tension better than does iridencleisis, over a longer postoperative period. Tension was controlled under 25 mm. Hg (Schiøtz), with and without miotics, in 46 percent of the 597 eyes following iridencleisis, and in 78 percent of 573 eyes following iridocorneosclerectomy. (Complete results will be published later.)

In addition to the fact that tension was controlled in fewer eyes following iridencleisis as compared with iridocorneosclerectomy, the diminution of efficacy in controlling tension following iridencleisis occurs much earlier and to a greater degree than that observed following iridocorneosclerectomy.

Only a minimum of complications were in 549 retained eyes observed for from one to 30 years. Of the more serious complications, atrophy of the globe occurred in one eye and phthisis bulbi in two eyes; hyphema, just over one percent; retinal detachment, one eye; cataract (not observed preoperatively) in three percent; and absolute glaucoma developed in one percent of the 549 eyes following iridocorneosclerectomy.

TABLE 3

Complications following iridocorneosclerectomy in 549 retained eyes observed for from one to 30 years postoperatively

Complication	No. of Eyes
Atrophic globes	1
Phthisis bulbi	2
Absolute glaucoma	6—1%
Iritis	2
Iridocyclitis	3
Uveitis	4
Vitreous prolapse	1
Cataract (not present before surgery)	14—3%
Hyphema (anterior chamber more than half full of blood)	8—1+%
Synechias	2
Retinal detachment	1
Choroidal detachment (1 with flat anterior chamber corrected by air injection and revision of wound)	3

One percent of the 556 retained eyes became atrophic following iridencleisis and phthisis bulbi occurred in an additional two percent. Postoperative cataract (not observed preoperatively) developed in four percent; dislocation of the lens, four percent; and hyphema in eight percent of this series of 556 eyes. Sympathetic ophthalmitis was reported in two eyes and severe uveitis* which was considered to be sympathetic ophthalmitis, occurred in an additional two eyes.

Summary

A statistical survey of 573 eyes with all types of glaucoma, treated with iridocorneosclerectomy and observed for from one to 30 years, revealed that tension was controlled (under 25 mm. Hg Schiøtz) in 34 percent without miotics and in 44 percent with miotics for a total of 78 percent in which the tension was controlled. Only 11 percent of

* Courtesy of Dr. F. Adler.

597 eyes observed for from one to 18 years was controlled without miotics following iridencleisis and 35 percent with miotics, for a total of 46 percent in which the tension was controlled.

Iridocorneosclerectomy was used as a primary operation in 91 percent of 436 eyes affected with chronic simple glaucoma. Of these, tension was controlled without miotics in 35 percent and with miotics in 45 percent, making a total of 80 percent of the eyes in which tension was controlled under 25 mm. Hg. In 78 eyes with acute glaucoma, iridocorneosclerectomy was used as a primary operation in 94 percent of the eyes and tension was controlled with and without miotics in 65 percent of this group. In 28 eyes with glaucoma secondary to uveitis, tension was controlled in 86 percent with and without miotics and in 26 aphakic eyes, tension was controlled in 58 percent (under 25 mm. Hg Schiøtz).

The efficacy of filtering operations diminishes with time, with more reoperations required to control tension. However, following iridocorneosclerectomy, tension is controlled over a longer postoperative period with fewer secondary procedures than following iridencleisis. In 197 eyes observed for from one to six years following iridocorneosclerectomy, tension was controlled with and without miotics in 88 percent, and a secondary procedure was required in only six percent of these eyes. In a total of 197 eyes observed for from seven to 11 years, 80 percent of the eyes was controlled following iridocorneosclerectomy, a loss of eight percent over the shorter postoperative period, and 21 percent of this second group required additional surgery.

In a series of 179 eyes observed for from 12 to 30 years following iridocorneosclerectomy, 64 percent of the eyes were controlled with and without miotics, with additional surgery required in 37 percent of these eyes. This consists of a loss of 16 percent of efficacy over the first group.

A minimum number of complications were observed following iridocorneosclerectomy in 549 retained eyes observed over a period of from one to 30 years. Atrophy of the globe occurred in one eye; phthisis bulbi in two eyes, absolute glaucoma developed in one percent; iridocyclitis in three eyes; iritis in two eyes; vitreous prolapse in one eye; cataract not noted preoperatively in three percent; marked hyphema in plus-one percent; retinal detachment in one eye and extensive detachment of the choroid in two eyes.

Atrophy of the globe occurred in one percent and phthisis bulbi in two percent of 556 eyes observed for from one to 18 years following iridencleisis in retained eyes. Absolute glaucoma developed in three percent; iridocyclitis in one percent; uveitis in two eyes, severe uveitis (possibly sympathic ophthalmitis) in two eyes and definitely established sympathetic ophthalmitis in an additional two eyes. Cataract, not noted preoperatively, occurred in four percent of the retained 556 eyes, and disclocated lens in an additional four percent; retinal detachment in three eyes; marked hyphema in eight percent and retrobulbar hemorrhage in two eyes, constitute some of the more serious complications encountered following iridencleisis.

Conclusion

The choice of an operative procedure for the control of tension in glaucoma should be carefully considered not only for its mode of action, but also for the over-all long-range performance of the operation. The evaluation of the procedure should include the control of tension within normal limits without and with the use of miotics, the increase or preservation of the preoperative visual fields and visual acuity postoperatively, and the immediate and long range postoperative complications.

The technique of iridocorneosclerectomy may be slightly more difficult and more time consuming than other filtering operations,

particularly iridencleisis, but the excellent long-lasting results with a minimum of complications reported in 573 eyes observed over a period of from one to 30 years, suggest strongly that iridocorneosclerectomy warrants the additional effort required.

708 Park Avenue (21).
13 Walnut Road.

References

1. Lagrange, F.: Iridectomie et sclerectomie combinees dans le traitement du glaucome. Arch. d'ophtal., **26**:481, 1906.
2. Holth, S.: Sclerectomie avec la pince emporte-piece dans le glaucome, de preference apres incision a la pique. Ann. d'ocul., **142**:1, 1909.
3. Elliot, R. H.: A preliminary note on a new operative procedure for the establishment of a filtering cicatrix in the treatment of glaucoma. Ophthalmoscope, 1909, p. 804.
4. Berens, C.: Iridocorneosclerectomy for glaucoma. Am. J. Ophth., **19**:470 (June) 1936.
5. Berens, C., Sheppard, L. B., and Duel, A. B., Jr.: Cycloelectrolysis for glaucoma. Am. J. Ophth., **34**:53 (Jan.) 1951; Tr. Am. Ophth. Soc., **47**:364, 1949.
Berens, C.: The surgery of glaucoma: Cycloelectrolysis vs. Cyclodiathermy Acta XVI Conc. Ophth. (Britannia) 1950, p. 595.
———: Glaucoma surgery: An evaluation of cycloelectrolysis and cyclodiathermy. A.M.A. Arch. Ophth., **54**:548 (Oct.) 1955.
Berens, C., and Sheppard, L. B.: Clinical and experimental considerations of cycloelectrolysis and cyclodiathermy. XVIII. Intern. Congress, Brussels, Belgium 1958 (in press).
6. Stallard, H. B.: Eye Surgery. Baltimore, Williams & Wilkins, 1958, p. 624.
7. Berens, C., and Tolman, C.: Bulbar compressors; Bilateral bulbar compression in the diagnosis and management of glaucoma. Am. J. Ophth., **47**:187 (Feb) 1959.
Duke-Elder, S.: Provocative tests in glaucoma: The bulbar pressure test. Glaucoma Symposium. Springfield, Ill., Thomas, 1955, p. 245.
8. Scheie, H. G.: Retraction of scleral wound edges as a fistulizing procedure for glaucoma. Am. J. Ophth., **45**:220 (Apr.) 1958.
9. Berens, C.: Curved knives for sclerectomy operations for glaucoma. Am. J. Ophth., **24**:804 (July) 1941.
10. ———: Special suturing and fixation forceps. A.M.A. Arch. Ophth., **48**:348 (Sept.) 1952.
11. A curved (hollow ground) keratome for sclerectomy operations. Am. J. Ophth., **18**:1053 (Nov.) 1935.
12. Chandler, P. A.: Round table conference: Glaucoma. New York Soc. Clin. Ophth., Am. J. Ophth., **40**:575, 1955.

THE INCIDENCE OF GLAUCOMA IN DIABETES MELLITUS*

A comparison with the incidence of glaucoma in the general population

John R. Armstrong, M.D., Ray K. Daily, M.D., Harold L. Dobson, M.D., and Louis J. Girard, M.D.
Houston, Texas

Introduction

In following patients of the diabetic clinic of Jefferson Davis Hospital, a high incidence of concurrent ocular disease was noticed. It was well known, of course, that such conditions as cataract, diabetic retinopathy, rubeosis iridis, venous thrombosis, and hemorrhage occurred much more frequently in diabetics than in nondiabetics; however, it seemed that diagnoses of glaucoma also appeared more often among the diabetics of our clinic than might be expected in nondiabetics. When standard texts on ophthalmology and on diabetes were examined there was no mention of an increased incidence of glaucoma in diabetes; therefore, a more extensive survey of the available literature was done.

In order that a proper comparison might

* From the Departments of Ophthalmology and Internal Medicine, Jefferson Davis Hospital, and Baylor University College of Medicine. This study was supported in part by a grant from the Knights Templar Eye Foundation, Inc.

be made between the diabetic and nondiabetic populations, the reported incidence of glaucoma in the nondiabetic population was ascertained. Information regarding the absolute incidence of all the glaucomas in the nondiabetic population was difficult to find; however, a number of authors has contributed statistics pertaining to the incidence of primary chronic glaucoma. These percentages range from 0.02 percent (Kogoshima, 1915[1]) to 15.7 percent (Pilman, 1927[2]).

Recent mass screening surveys have given figures between these extremes. Brav and Kirber in 1956[3] found an incidence of 2.24 percent of borderline to definite glaucoma. The Cleveland Glaucoma Survey in 1953[4] reported an incidence of about two percent. Horsley, Lewis and Packer in 1958[5] found by routine tonometry that four percent of 1,210 patients over 40 years of age in an out-patient department had unrecognized glaucoma. Carvill in 1932[6] reported an incidence of 1.35 percent (primary and secondary) found in 30,000 patients admitted to the eye out-patient department of the Massachusetts Eye and Ear Infirmary. It is generally accepted that the average incidence of primary glaucoma in the general population is about one to two percent.[7]

Some difficulty was encountered in attempting to find adequate studies concerning the incidence of glaucoma in diabetes mellitus. In 1956, Palomar[8] published a review of the literature which included some of his own work. He stated that chronic simple glaucoma does not occur more frequently in diabetes mellitus than in the general population; in fact routine tonometry gives a lower average tension in diabetics. He included 416 diabetics in his study.

Waite and Beetham in 1935[9] reported a study of the visual mechanism in 2,002 diabetics, using refractions, peripheral fields, central fields, slitlamp examinations, funduscopies and the Schiøtz tonometer (the type of calibration scale used was not mentioned), in which only 0.5 percent had "clinical glaucoma" (including primary and secondary). On examining their figures, however, it is seen that approximately 6.0 percent of the eyes examined had tensions greater than 25 mm. Hg.

Leydhecker, et al.,[10] in an effort to determine normal intraocular pressure, recently found that, after taking ocular tensions of 10,000 normal people, only 2.3 percent exceeded 20.5 mm. Hg, and that in cases of tensions greater than this glaucoma should be suspected and investigated. Only 0.14 percent exceeded a pressure of 23.2 mm. Hg. They concluded that pressures of 26.5 mm. Hg and over are definitely pathologic.

The disparity of statistics by the authors just mentioned and the aforementioned clinical impression stimulated interest in further investigation and a study, designed to illuminate any relationship between glaucoma and diabetes, was undertaken.

Method of procedure

The investigation consisted of five parts: (1) a study of unselected diabetics for glaucoma, (2) a study of a control group of the general clinic population for glaucoma, (3) a review of diabetic clinic charts for diagnoses of glaucoma, (4) a review of glaucoma clinic charts for the incidence of diabetes, and (5) blood glucose and urine sugar determinations on an unselected group of glaucoma patients.

In order to determine the incidence of glaucoma in diabetics, tonometry was used as the major screening test.[3-5] A standardized Schiøtz tonometer with the 1955 calibration scale of the Committee on Standardization of Tonometers was used.

There is little agreement as to the dividing point between normal tensions and those suspicious of glaucoma. Brav and Kirber[3] in their recent study considered those tensions over 25 mm. Hg suspicious, whereas Leydhecker, et al.,[10] now believe tensions of more than 20.5 mm. Hg to be suspicious of glaucoma and 26.5 mm. Hg to be definitely

pathologic. Sugar[7] states that tensions of 24 mm. Hg are suspicious and that tensions of 25 mm. Hg are usually pathologic.

In view of these differences it was decided to use 23.4 mm. Hg as our dividing point, and patients found to have ocular tensions of 23.4 mm. Hg or greater were rechecked two or more times at later dates. If their tensions remained over 23.4 mm. Hg at least three times they were scheduled for more complete glaucoma workups.

This study contains 393 unselected diabetics (approximately 38 percent of the diabetic clinic census). All these patients had been previously diagnosed as diabetic by the usual criteria involving both clinical and laboratory data.

A control group of 280 patients from the general medicine out-patient department also had ocular tensions checked and were scheduled for glaucoma workup according to the criteria just described. The patients selected corresponded in age, sex, and color with those in the diabetic clinic, as determined by means of a recent analysis by Dobson, et al.,[11] of this same diabetic clinic population.

A total of 844 diabetic clinic charts (81 percent of the diabetic clinic population) were reviewed with reference to eye clinic records, previous tensions taken for diagnoses of glaucoma, and the type of glaucoma diagnosed. The entire glaucoma clinic population of 325 charts was reviewed for the incidence of diabetes mellitus, dates of diagnoses of both diabetes and glaucoma, and the type of glaucoma diagnosed.

Fifty-three glaucoma patients, unselected except for the exclusion of known diabetics, had blood glucose determinations done by the tape method[12] and urinalyses for reducing substances. These tests were performed without regard to previous food ingestion, and so fasting and nonfasting patients are included. Those patients with blood glucose levels greater than 150 mg. percent and/or positive urines were given further diagnostic tests for diabetes mellitus, including fasting blood sugar and glucose tolerance tests.

Results

Of the 393 diabetic patients who had tonometry, 34 either were scheduled for workup in the glaucoma clinic or, if known glaucoma patients, with ophthalmologic workups completed, their hospital charts were reviewed. Eleven undiagnosed glaucoma cases were detected by the tension check. In three of these 34 cases the examination was not completed because of death, and in two the diagnosis of glaucoma was inconclusive. These were eliminated from the study. Three patients were proved subsequently not to have glaucoma. In 26 patients the diagnosis of glaucoma was established. Each case is summarized in Table 1 and, in the cases of secondary glaucoma, the etiologic factor is listed. This is an over-all incidence of 6.6 percent glaucomatous patients in the diabetic clinic.

The incidence of the various types of glaucoma is shown in Table 2: The incidence of primary glaucoma is 4.8 percent of diabetics and that of primary chronic glaucoma is 4.1 percent. Fourteen of the 26 glaucoma patients (57 percent) had cataracts. Senile cataracts were not differentiated from diabetic cataracts. Four of the glaucoma cases developed subsequent to cataract extractions.

An attempt was made to correlate the dates of diagnoses of diabetes and glaucoma in each case, though obviously this would be subject to many extraneous variables which would decrease the statistical validity of the data. In 17 cases (65 percent) the diabetes was diagnosed first, an average of 6.9 years before diagnosis of the glaucoma. Four cases were diagnosed in the same year. In five cases glaucoma was diagnosed first (19 percent), averaging two years before diagnosis of diabetes.

Ten patients from the control group of 280 nondiabetics were scheduled for glau-

TABLE 1

DIABETIC PATIENTS WITH PROVEN GLAUCOMA

No.	Hospital No.	Age (yr.) Sex Race	Year Diabetes Diagnosed	Year Glaucoma Diagnosed	Corrected Visual Acuity O.D./O.S.	Tension (mm. Hg, Schiøtz) O.D./O.S.	Central Fields	Provocative Tests	Tonography O.D./O.S	Type Glaucoma	Fundi	Addenda
1	AV601	69 C/F	1951	1955	20/20 / 20/20	30/30	Slight constriction	Water+	C=0.18/0.12	Primary non-congestive	Normal	Open angle
2	TT1443	70 C/F	1950	1965	20/50 / 20/40	37/34	Minimal loss			Primary non-congestive	Mild retinopathy	Immature cataract (O.U.) Repeated high tensions Open angle
3	MM9000	77 C/F	1958	1958	NLP / 20/20	58/30	NLP (O.D.) Moderate loss (O.S.)		C=0.06/0.08	Primary non-congestive		Cataract (O.U.) Narrow angle
4	KK3928	55 C/M	1956	1956	NLP / 20/200	37/37	Normal			Primary non-congestive	Cupping IV retinop.	Repeated high tensions Open angle
5	CE3595	70 C/M	1957	1958	20/50 / 20/50	32/27	Moderate loss		C=0.08/0.06	Primary non-congestive	Cupping	Cataract (O.U.), open angle Repeated high tensions
6	JJ7655	66 C/F	1954	1956	Pthisis / H.M.	Pthisis / 40				Primary non-congestive	Cupping II retinop.	Cataract, immature (O.S Open angle O.S.
7	XX2247	82 W/F	1956	1958	NLP / 20/50	39/36				Primary non-congestive	Cupping	Cataract (O.U.) Open angle
8	SS2388	64 C/F	1957	1958	20/50 / 20/100	33/31	Moderate loss	Water− Mydriasis−	C=0.06/0.10	Primary non-congestive	No cupping no retinop.	Repeated high tensions Open angle
9	GG1083	57 C/F	1941	1958	20/20 / 20/20	31/34	Moderate Constriction		C=0.15/0.07	Primary non-congestive	II retinop.	Repeated high tensions Open angle
10	AL6281	72 C/F	1949	1959	20/70 / 20/30	28/33	Moderate Constriction			Primary non-congestive	Cupping	Immature cataract (O.U.) Open angle
11	AJ4506	67 C/M	1951	1949	NLP	54/60	NLP			Primary non-congestive	Cupping	Repeated high tensions Open angle

12	AG7785	61 C/F	1957	1956	20/30 / 20/20	32/34	Normal	Water+		Primary non-congestive	Mild retinop.	Open angle
13	AS6568	68 C/F	1951	1958	20/100 / 20/100	26/33		Water+		Primary non-congestive	IV retinop.	Cataract, immature (O.U.) Open angle
14	DE6048	63 C/F	1948	1957	20/200 / 20/200	27/32	Much constriction			Primary non-congestive	II retinop.	Cataract, immature (O.U.) Narrow angle
15	OO4870	60 C/F	1957	1959	20/80 / 20/200	25.8 / 29		Water+	C = 0.10 / 0.07	Primary non-congestive	Cupping	Cataract, immature (O.U.)
16	AP509	63 W/F	1955	1959		29 / 38.9		Water+		Primary non-congestive	II retinop.	Open angle
17	VV6347	69 W/F	1931	1956	20/20 / 20/20	30/40	Minimal loss	Water+		Primary congestive	Normal	Repeated high tensions Very narrow angle
18	GG3726	52 C/F	1953	1951	10/200 / 20/40	43/37	Moderate loss		C = 0.12 / 0.15	Primary congestive	Cupping	Cataract (O.U.) Very narrow angle
19	AT1470	66 C/F	1954	1954	10/200 / C.F.	46/40	Unreliable			Primary congestive	Cupping	Cataract (O.U.) Angles closed
20	CE239	37 W/M	1933	1953	ENU/ENU	62/?	ENU (O.U.)			Secondary	Mild retinop.	Rubeosis iridis
21	AF8641	73 W/M	1955	1958	NLP / 20/25	53/12				Secondary		Thrombosis central retinal vein
22	CF6552	54 C/F	1956	1958		12/70				Secondary		Dislocated lens
23	DD1897	54 C/F	1956	1954		61/53	NLP (O.U.)			Secondary	Not visible	Cataract extraction (O.U.)
24	AE4545	50 W/F	1947	1947	20/30 / NLP	28/50	Constriction (O.D.) NLP (O.S.)			Secondary	No cupping No retinop.	Cataract extraction (O.U
25	AZ4766	64 W/F	1954	1952	NLP	62/30	NLP			Secondary	I. retinop.	Cataract extraction (O.U.)
26	OO4493	70 W/F	1954	1957	?/NLP	13/58				Secondary		Cataract extraction (O.S.)

TABLE 2

INCIDENCE OF VARIOUS TYPES OF GLAUCOMA

	Primary Glaucoma			Secondary Glaucoma			Over-all
	Noncongestive	Congestive	Total	Extraction	Other Factors	Total	
Number of Cases	16	3	19	4	3	7	26
Percent of Diabetic Population	4.1%	0.76%	4.8%	1.0%	0.76%	1.8%	6.6%

coma workups. Three of these were known to have glaucoma. Two of the remaining seven were subsequently proved not to have glaucoma. The diagnosis of glaucoma was established in eight patients, giving an overall incidence of glaucoma of 2.8 percent in the general population. Seven of these (2.5 percent) were found to have primary glaucoma, of which four (1.4 percent) were primary chronic glaucoma. One case was secondary to radiation therapy of a squamous-cell carcinoma of the conjunctiva. These cases are tabulated in Table 3.

Of the 844 diabetic clinic charts reviewed, 192 cases were found that had been examined and had ocular tensions taken in the eye clinic (the measurement of tensions is ordinarily a routine part of the examinations of older persons in this eye clinic). Forty-nine patients had the diagnoses of glaucoma established in the glaucoma clinic. These are shown in Table 4. Those cases classed as

TABLE 3

CONTROL PATIENTS WITH PROVEN GLAUCOMA

Number	Hospital Number	Age (yr.), Sex, Race	Type of Glaucoma	Tension (mm. Hg, Schiøtz) O.D./O.S.	Diagnostic Tests
1	AG8823	69 C/F	Secondary	17/46	396 r for squamous-cell carcinoma of conjunctiva (O.S.)
2	FF8779	59 C/F	Primary congestive	35/30	Positive mydriasis test; facility $-\frac{0.12\text{ (O.D.)}}{0.11\text{ (O.S.)}}$
3	JJ1409	65 C/F	Primary congestive	34/37	Repeated high tensions; facility $-\frac{0.04\text{ (O.D.)}}{0.06\text{ (O.S.)}}$
4	CE3190	53 C/M	Primary congestive	97/38.9	Positive dark room test; typical field changes
5	K7462	65 W/F	Primary noncongestive (open-angle)	46/46	Positive water test; typical field changes; repeated high tensions
6	CE1747	50 C/F	Primary noncongestive (open-angle)	30/28	Borderline water test; repeated high tensions
7	AC9711	54 C/M	Primary noncongestive (open-angle)	33/33	Positive water test; repeated high tensions
8	AM1772	51 C/F	Primary noncongestive (open-angle)	25/30	Positive water test; repeated high tensions

TABLE 4

GLAUCOMA CASES FOUND IN DIABETIC CHART REVIEW

	Open-angle	Narrow-angle	Secondary	Unknown	Total
Number of cases	21	13	8	7	49
Percent of total charts reviewed	2.5%	1.5%	0.9%	0.8%	5.9%
Percent of charts with recorded tensions	10.9%	6.7%	4.1%	3.6%	25.3%

unknown are the cases in which differentiation between either primary and secondary glaucoma or open-angle and narrow-angle glaucoma was equivocal. These 49 cases constitute 26.0 percent of all patients with recorded tensions and 5.9 percent of all charts reviewed. These data are not adequate for the determination of a definite incidence of glaucoma in diabetes but indicate that the incidence is at least 5.9 percent and probably higher.

On reviewing the charts of the entire glaucoma clinic population of 325 patients, 41 or 12.6 percent were found to be diabetics. The data concerning dates of diagnoses of diabetes in glaucoma and the type of glaucoma are incomplete; however, they appear to indicate that diabetes was discovered first in a large majority of cases, and that chronic simple glaucoma was about twice as frequent as secondary glaucoma in these cases.

Of the 53 glaucoma patients tested for blood and urine sugar by the methods described, seven were found to have suspicious results, and three of these (5.7 percent) were subsequently proved to have diabetes. The small number comprising the test group precludes statistical validity of these results; however, they are indicative, at least, that the incidence of diabetes is even higher than the figure of 12.6 percent described in the paragraph above.

DISCUSSION

As mentioned previously, the reported incidence of glaucoma varies widely; however, most investigators[7] concur that the incidence of chronic simple glaucoma in the general population is in the range of one to two percent. The incidence for the control group in this study is 1.4 percent. Figures from this study on the incidence of glaucoma in diabetics do not agree so closely, however, with previous studies. Palomar,[8] in a comprehensive review, states that chronic simple glaucoma does not occur more frequently in diabetics than in the general population, and that it is generally known that routine tonometry gives a lower average tension in diabetics. Waite and Beetham, in a large series reported in 1935,[9] gave an incidence of 0.5 percent glaucoma in diabetics. Our overall incidence of 4.1 percent primary chronic glaucoma in diabetics is almost three times as high as was found in our control population and twice that reported in most studies of the general population.

The 12.6-percent incidence found in the records of the patients of the glaucoma clinic is actually higher, since an additional 5.7 percent of glaucoma patients had previously undiagnosed diabetes. This, together with the increased incidence of glaucoma in diabetics as already shown, constitutes justifiable evidence to support the conclusion that there is a relationship between glaucoma and diabetes, and that clinical diabetes is likely to occur before glaucoma, since diabetes was diagnosed before the glaucoma in a significant majority of our cases. The evidence presented would seem to indicate that diabetes predisposes to development of glaucoma.

The anatomic and physiologic causes for increased intraocular pressure in cases of secondary glaucoma are usually self-evident.

The higher incidence of secondary glaucoma can be attributed to the well-known increased frequency of cataracts in diabetics with the increased number of complications following intraocular surgery, the occurrence of rubeosis iridis, the increased frequency of venous thrombosis, and other factors.

The etiology of primary glaucoma, particularly the primary chronic type, is less clear. It is obvious that in an eye with a shallow anterior chamber and narrow angle, mechanical blockage of aqueous flow might occur with subsequent increased intraocular pressure. There is no agreement on the pathogenesis of glaucoma in an eye with no gross anatomic abnormality, however. There have been many theories put forth in an effort to explain this type of glaucoma.

Becker stated in a review of glaucoma in 1956[13] that the site of resistance to aqueous outflow was variously thought to be in the trabeculae, aqueous veins draining immediately from the canal of Schlemm or in the communicating vessels in their oblique course through the sclera.

Elwyn[14] has stated that primary glaucoma is a strictly functional disease of the parasympathetic nervous system, and that addition of organic change occurs later. He quotes Duke-Elder as stating that a significant number of patients with chronic simple glaucoma have general vascular instability. In this connection Dienstbier, et al.,[15] state that emotional factors operating on the autonomic nervous system have a definite influence on tension in the eye.

Duke-Elder[16] also has said that primary glaucoma is not a local disease of the eyes but an eye complication of some unknown organic or systemic disturbance. Friedenwald[17] has suggested that "open-angle glaucoma may consist in an inability to suppress (an) enhanced resistance to outflow."

Recent experimental work by Christiansson[18] has led to very interesting results. He did studies of the intraocular pressure in rabbits made diabetic with alloxan. The diabetic rabbits, studied over a period of many weeks, were found to have decreased intraocular pressure in general; however, the diabetes so affected the facility of outflow, as determined by tonography, that it was reduced by 43 percent. This author attributed this to an abnormal deposit of a mucopolysaccharide in the trabecular network.

The frequent ocular venous hemorrhages and capillary aneurysms seen in diabetics are also thought to be due to an abnormal polysaccharide deposition which weakens the vessel walls (Schlossman, 1956). When insulin was given to the rabbits, and the blood sugar level returned to normal, the tensions also returned to normal, but the facility of outflow remained low.

Christiansson conjectures a possible homeostatic mechanism in the normal eye that suppresses formation of aqueous in case of any blockage decreasing the facility of outflow.

If one can accept the theory that chronic simple glaucoma has a higher incidence in diabetics than in nondiabetics, an explanation of this difference might be that there are persons without the properly functioning homeostatic mechanism just suggested, but without obstruction to the outflow of aqueous, therefore with no increased intraocular pressure. On the development of diabetes with the resultant reduced facility, found experimentally (see Christiansson), these persons might well be unable to compensate for the reduced outflow and would therefore develop increased intraocular pressure.

In following this line of thought it can be theorized that there are certain people who have a predisposition to chronic simple glaucoma for reasons suggested by Friedenwald above, and that occurrence of any one of various unrelated factors causing increased resistance to aqueous outflow, including diabetes, might be sufficient to cause eventual development of this condition. The genetic influences concerning predisposition to primary glaucoma are well known.[13]

Summary and Conclusions

The incidence of glaucoma in a group of 393 unselected diabetics was determined with the use of a standardized Schiøtz tonometer as the major screening test. Those patients with suspicious tensions were referred to the glaucoma clinic of Jefferson Davis Hospital for further studies. Of the 393 diabetics, 4.1 percent were found to have primary, noncongestive glaucoma, and 1.8 percent were found to have secondary glaucoma. In a majority of cases, diabetes was discovered before glaucoma.

Two hundred and eighty patients from the general medicine out-patient department, selected to correspond with the diabetic patients as to age, sex and color, were tested in a like manner. Of these, 1.4 percent were found to have primary, noncongestive glaucoma, and 0.36 percent were found to have secondary glaucoma.

A total of 844 diabetic clinic charts were reviewed. The over-all incidence of glaucoma was found to be at least 5.9 percent of the diabetics. Of 325 clinic charts reviewed, 12.6 percent were found to be of diabetics. In a majority of cases, diabetes was discovered before glaucoma.

Fifty-three glaucoma patients, unselected except for exclusion of known diabetics, had blood glucose determinations done by the tape method and urinalyses for reducing substances. Those patients with blood glucose levels of greater than 150 mg. percent and positive urines were given further diagnostic tests for diabetes mellitus. Of the 53 patients, 5.7 percent were found to have previously unsuspected diabetes.

The evidence presented suggests that the incidence of both primary and secondary glaucoma in diabetes is appreciably increased over that in the general population. This indicates that diabetics with any suspicious visual complaints should be considered for glaucoma testing, and that glaucoma patients with symptoms even mildly suggestive of diabetes be given routine sugar metabolism studies.

703 Hermann Professional Building.

References

1. Cited by Sugar.[7]
2. Cited by Duke-Elder, W. S.: Textbook of Ophthalmology. St. Louis, 1941, Mosby Co., v. 3.
3. Brav, S. S., and Kirber, H. P.: Mass screening for glaucoma. J.A.M.A., **147**:1127, 1956.
4. Wolpaw, B. J., and Sherman, A. W.: The Cleveland glaucoma survey. Sight-Saving Review, **24**:139, 1954.
5. Horsley, H., Lewis, P., and Packer, H.: Glaucoma detection in an outpatient department. J.A.M.A., **166**:1265, 1958.
6. Carvill, M.: A review of cases of glaucoma admitted to the Massachusetts Eye and Ear Infirmary over a period of two years. Tr. Am. Ophth. Soc., **30**:71, 1932.
7. Sugar, H. S.: The Glaucomas. New York, Hoeber, 1957.
8. Palomar Palomar, A.: Ophthalmological manifestations of diabetes mellitus. Arch. soc. oftal. hispano-am., **16**:827, 1956.
9. Waite, J., and Beetham, W.: The visual mechanism in diabetes mellitus. New England J. Med., **212**: 367 and 429, 1935.
10. Leydhecker, W., Akiyama, K., and Neumann, H.: Der intraokulare Druck gesunder menschlicher Auge. Klin. Monatsbl. f. Augenh., **133**:662, 1958.
11. Dobson, H. L., Lipscomb, H. S., Greene, J. A., and Engelhardt, H. T.: Socioeconomic status and diabetes mellitus. J. Chronic Dis., **7**:413, 1958.
12. Lipscomb, H. S., Bean, J., Dobson, H. L., and Greene, J. A.: The determination of blood sugar. Diabetes, **7**:486, 1958.
13. Becker, B.: Glaucoma: 1955-1956. Arch. Ophth., **56**: 1956.
14. Elwyn, H.: The problem of glaucoma. Am. J. Ophth., **33**:1373, 1950.
15. Dienstbier, E., Balik, J., and Kafka, H.: A contribution to the theory of vascular origin of glaucoma. Brit. J. Ophth., **34**:47, 1950.
16. Cited by Dienstbier, et al.[15]
17. Cited by Christiansson.[18]
18. Christiansson, J.: Studies of intraocular pressure in diabetes (alloxan) in rabbits. Acta Ophth., **36**:163, 1958.

TOXIC RETINOPATHY*

With vascular proliferation and hemorrhage into the vitreous in an asthmatic patient being treated with arsenic

Louis E. Prickman, M.D., Robert W. Hollenhorst, M.D., and Ernst O. Ammermann, M.D.
Rochester, Minnesota

> Inorganic arsenic is capricious, unpredictable, and uncontrollable both as to good and harm, but the harm is more certain and generally more frequent than the good.
> —Sollmann[1]

Arsenic is one of the oldest recorded remedies for the treatment of asthma. The great encyclopedist of the first century, Pliny[2] the Elder, recorded such use of arsenic. As an agent for the symptomatic treatment of asthma, arsenic has persisted through the centuries and is still used today.[3] Although it may be an effective symptomatic remedy for some patients with asthma, the serious toxic effects and complications that often result contraindicate its use, particularly since arsenic therapy is not curative, and also because other symptomatic remedies are safer and are equally effective. According to Goodman and Gilman,[4] arsenic acts in the body by blocking the sulfhydryl enzyme systems in the cells, forming tissue protein-thioarsenites. Since sulfhydryl enzyme systems are vital to all cellular metabolism, chronic arsenic poisoning may affect any body structure.

The onset of symptoms arising from chronic arsenic poisoning, especially from low therapeutic doses, is quite variable. In Hansen-Pruss's[5] series of 17 cases, symptoms developed in one patient after two weeks of treatment. In others, the onset of more serious symptoms was delayed as long as two and one-half years. Many patients take the medicine for three or more years without noticing any symptoms. This does not mean that the patient has not been affected by arsenic; rather it means that no recognized changes have taken place. Butzengeiger,[6] Roth[7] and others have described patients ingesting arsenic up to eight years or more before toxic effects were noted. There is apparently no consistent relationship between the amount of arsenic ingested or the length of treatment and the time of onset or the severity of a patient's symptoms. Therefore, individuals vary greatly in their tolerance to this drug. The following case illustrates how potassium arsenite (Fowler's solution) may relieve the symptoms of asthma, at least temporarily, but it also illustrates some of the serious toxic manifestations of such arsenic therapy.

Report of case

A 32-year-old man came to the Mayo Clinic on September 15, 1952, because of sinus trouble and asthma. Twelve years previously, on entering the Army, he had noticed the onset of postnasal discharge and stuffiness of the nose. These difficulties had continued since then, and were worse in cold, damp weather. At about the same time, he began to have symptoms of asthma for which he received several types of medication. For two years prior to admission to the clinic, he had taken Gay's[8] red liquid medicine, which is reported to contain Fowler's solution and other substances. Also, four months before entering the clinic, he had taken a preparation of corticosteroids for four to five weeks, with which he obtained some symptomatic relief.

On examination, the patient's skin was pigmented in the speckled raindrop variety characteristic or suggestive of arsenical origin, and he had keratoses on the feet and one small keratosis on the right index finger, consistent with arsenism. No oral pigmentation was seen and there was no increase in pigmentation in the flexor areas or over the extensor aspects of the joints or in an abdominal scar. There was no loss of strength or other findings to suggest addisonism.

The nasal mucous membrane was infected and boggy, and pus was seen on both middle turbinates. Polyps were present in the left middle meatus.

* From the Section of Medicine and the Section of Ophthalmology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Roentgenograms showed cloudiness of the left antrum; antral lavage disclosed pus, grade 4. Surgical exenteration of the ethmoids and creation of a left antral window were advised.

Routine laboratory studies, including urinalysis and blood counts, and roentgenographic examination of the thorax gave negative results. The erythrocytic sedimentation rate was 34 mm. in one hour (Westergren). An allergic survey gave negative results except for questionable reactions to dog hair, cattle hair, feathers and house dust. Because of the appearance of his skin, the question of Addison's disease had been raised previously in a veterans' hospital, but the results of a water test there had been reported as negative. In the same hospital, arsenic was found in an area of excised skin. At the Mayo Clinic the value for 17-ketosteroids in 24 hours was 6.0 mg. per 100 ml.

On September 18th, a nasoantral window was made, polyps were removed and the ethmoids were exenterated. The antrum contained creamy yellow pus and the mucous membrane was edematous. A small amount of excised membrane was examined by a pathologist and reported as showing inflammatory changes.

On September 23rd, the vision was 20/20 and 14/21 in each eye. The visual fields were normal to confrontation. Ophthalmoscopic examination showed several cotton-wool patches about the posterior pole of each fundus, a few scattered hemorrhages, and dilatation of the capillaries between the disc and the macula in each eye. These retinal lesions were interpreted as representing a toxic retinopathy. The possibility of underlying diabetes mellitus or collagen disease was considered by the ophthalmologist. However, the value for fasting sugar was found to be 95 mg. per 100 ml., and no supporting evidence of diffuse collagen disease was found.

The patient was warned against exposure to dust and feathers, was urged to avoid overcoughing, fatigue, respiratory irritants, smoking and colds, and was advised to return in two or three months for re-examination of the chest and ocular fundi. At the time of dismissal, his asthmatic condition was about 60 percent improved.

When the patient returned on January 15, 1953, his asthma was still troublesome; he had noticed blood in the sputum eight or 10 times and had been having nocturnal paroxysmal asthma with cough and expectoration of greenish-yellow material. In December he had had a severe cold with laryngitis and fever initiated by a chill.

On admission, his blood pressure, pulse and temperature were within normal limits. Musical rales were heard bilaterally in the chest, being louder in the right base. The appearance of the skin had not changed. The nasal mucosa appeared congested and red, and mucopus was present bilaterally. The mucous membrane of the left middle meatus and of the left antrum was edematous.

The vision and visual fields were still normal. Ophthalmoscopic examination revealed in each eye dilatation of the capillaries in the macular region and several soft exudates and clusters of newly formed capillaries in the retina nasal to each optic disc. There were irregularities in the caliber of several large veins in the retina of the left eye. Again, the possibility of diabetes was suggested by the ophthalmologist.

The value for fasting blood sugar was 115 mg. per 100 ml. A glucose-tolerance test done after excessive ingestion of carbohydrates for 36 hours gave normal results. At the time of the test, the value for fasting blood sugar was 100 mg. After this, 69 gm. of sugar was administered and one hour later the value for blood sugar was 168 mg.; two hours later, 100 mg.; and three hours later, 78 mg. The urine contained no sugar. X-ray examination of the chest gave negative results, and those of the sinuses showed pansinusitis with thickened membranes in the medial wall of each antrum.

Because of the history of hemoptysis, bronchoscopic examination was carried out, which showed a markedly inflammatory reaction throughout the bronchial tree. There was no evidence of stricture or purulent secretion. A small amount of mucoid secretion was aspirated for culture; this showed a green-producing streptococcus.

A week of treatment consisting of 1,000,000 units of penicillin given daily and lavage of the left antrum was carried out. Suction of the left ethmoid area showed a purulent condition which gradually subsided.

On January 21st, an acute cold developed and the patient was treated by rest in bed and inhalations of steam. The asthma was not aggravated by the cold. Musical rales, grade 1, were heard bilaterally.

At the time of dismissal the patient estimated that his asthmatic condition was 80 percent improved. He was advised to test his urine once a month, to have his fasting blood sugar estimated at home every four to six months, and to return to the clinic in six to 12 months for further evaluation of the eye findings and his asthma.

The patient returned on May 27, 1958, stating that on January 6th of that year, after hard coughing, he had suddenly noticed disturbance of the vision of his left eye. A diagnosis of hemorrhage into the vitreous was made by his local ophthalmologist. He was advised to avoid physical exertion for six months. He had noticed no further trouble with this eye since January.

His nasal symptoms were less troublesome. His asthma was aggravated by exertion and cigarette smoke. He had had no severe attacks of asthma since June, 1957, although mild flares were prone to occur with or after colds. He had been taking steroids intermittently.

A thick discharge oozed from the left antrum, and a lesser amount from the right side of the nose. Lavage of the right antrum showed pus, grade 4.

Examination of the eyes disclosed that the corrected vision, which previously had been 20/20 in each eye, was 20/25 in the right eye and 20/40 in the left eye. The anterior chambers and lenses were clear. In the lower half of the vitreous of the left eye there was a great deal of white fibrinous ma-

terial, apparently the residual of the previous hemorrhage. In both eyes the retinal veins had a slightly irregular caliber with occasionally a little sheathing of the vessels around the narrowed segments. Near each macula, and especially above the right macula, the tiny venules were dilated and had clublike capillary microaneurysms on their terminal branches. In the inferior nasal sector of the right eye was a mass of proliferated capillaries and venules, which ramified over the surface of the retina. In this mass there were fairly large, blood-filled aneurysms about the size of the cross section of a large retinal vein. One of these was a large irregular aneurysm partially filled with clot and surrounded by transudate from the aneurysm. In the left eye there were similar findings nasal to the disc but the details were obscured by recent hemorrhage. There were patches of fibrin on the inferior nasal retina. The retinal lesions were interpreted as representing a proliferative retinopathy, probably of toxic origin, and possibly initiated by the rather prolonged ingestion of arsenic. The absence of cotton-wool patches or soft exudates suggested that the retinopathy was inactive, or at least less active than it had been at the time of the previous examinations. It was thought probable that the recent bleeding had resulted from rupture, induced by excessive coughing, of the thin-walled newly formed vessels.

The appearance of the pigmentation of the skin had not changed, but a new finding was a goiter which was firm and finely nodular and suggested Hashimoto's thyroiditis. The patient appeared to be euthyroid, no bruits were heard, the basal metabolic rate was minus-one percent and the erythrocytic sedimentation rate (Westergren method) was 8.0 mm. in one hour. Iodide goiter was also suspected inasmuch as the patient had taken an iodine-containing antiasthmatic mixture two to four times daily for six years, until May 28, 1958. Needle biopsy of the thyroid showed colloid goiter. The patient was instructed to take 1.0 gr. of desiccated thyroid for a period of six months, after which he was to return for re-evaluation.

On June 2, 1958, a nasoantral window was made on the right side under local anesthesia. The lining membrane was polypoid and was curetted. The patient received tetracycline (achromycin V), 250 mg. four times daily before and after operation, and was advised to continue this medication for a week after he returned home. At the time of dismissal on June 6th, the window was open and contained no pus, and the asthmatic condition seemed remarkably improved.

The consultants who saw the patient with regard to his asthma were impressed with his tendency to overcough. He coughed "all the time," and hard, and had raised clear to yellow sputum with occasional flecks of blood. Five months previously, the rupture of the retinal vessel in the left eye occurred during a hard coughing spell. The patient was therefore urged to make every effort to avoid unnecessary overcoughing as had been his practice. Also, because of the fragile veins and proliferated capillaries in the eyes, he was urged to avoid lifting, strenuous exertion, diving, water skiing, shotgun shooting of which he was very fond, and respiratory irritants which might provoke coughing.

The patient's next visit to the clinic, on October 10, 1958, was precipitated because he suspected a new hemorrhage in the left eye following an episode of hard coughing a week previously. Also, his referring physician wrote that after giving him steroids recently for asthma, urinalysis disclosed sugar for the first time, and steroid therapy was promptly discontinued.

The patient was mildly asthmatic at night and on exertion. The right antrum felt sore and contained a micrococcus and nonpathogens. Lavage of the sinuses and tetracycline therapy cleared them of mucopus.

On October 10th, the vision was 20/25 and 20/50 and the fields were normal. The neovascularized areas and the aneurysms in the retinal veins were unchanged, but the retinal hemorrhage noted five months before had absorbed (figs. 1 and 2).

The value for fasting blood sugar was 123 mg. per 100 ml. Urinalysis did not reveal sugar. After the method of Conn, a glucose-tolerance test was done; 62.5 mg. of cortisone was given eight and one-half and repeated two hours before 77 gm. of dextrose were administered. The value for blood sugar after fasting was 119 mg.; after one hour it was 208 mg.; after two hours, 223 mg.; and after three hours, 107 mg. Grade 2 glycosuria was present. Later, a conventional glucose-tolerance test without prior administration of cortisone gave the following results: fasting blood sugar 119, after one hour 229, after two hours 111, and after three hours 72 mg., with grade 1 glycosuria. A diagnosis of mild diabetes seemed established for the first time, although it had been looked for a number of times during the previous six years he had been under observation. None of the patient's family or ancestors were known to have diabetes. The patient was 5 feet 8 inches tall and weighed 170 pounds (a little more than the average for his height).

Clippings of the nails and hair of the patient were examined for arsenic on this visit; the hair contained 10.24 mg. per 100 gm., the nails none.

The patient's final visit in June, 1959, was for the purpose of further treatment of his asthma, which had become almost intractable and required supplementary steroid therapy in the amount of 4.0 mg. of triamcinolone (Aristocort) four times daily. He had had no ocular symptoms, and ophthalmoscopic examination revealed vascular changes identical to those noted in October, 1958. Three additional observations were made at this time: there was no evidence of sinusitis, examination of the patient's hair and nails for arsenic gave negative results, and the value for "true" fasting blood sugar was 96 and 77 mg. on two occasions (normal "true" values being 65 to 90 mg. per 100 ml. of blood). Urinalyses were negative for sugar. At one

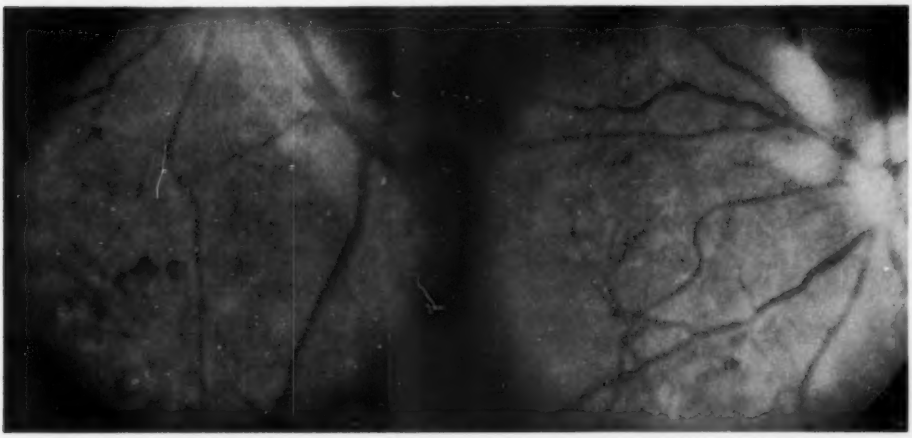


Fig. 1 (Prickman, Hollenhorst and Ammermann). Left eye. Inferior and nasal sectors of the retina of the left eye, with dilatation of the veins, capillary microaneurysms, and a patch of proliferated capillaries and venules with large aneurysms.

hour after 75 gm. of dextrose had been ingested the value for blood sugar was 179 mg., at two hours 140 mg., and at three hours 41 mg. In the interpretation of this test it is important to remember that the patient had been taking 16 mg. of Aristocort a day.

Comment

The cause of the retinal changes in this patient is not clear. Possibly, chronic arsenism contributed to its occurrence, and we shall discuss the evidence in support of this viewpoint. We shall also discuss the possibility that the lesions noted in the eyes were due either to latent or preclinical diabetes mellitus, or to infection in the form of chronic purulent sinusitis and chronic bronchitis. Perhaps all three factors contributed to the development of retinitis proliferans in this case.

Arsenism

Arsenic, particularly in the trivalent form, is a potentially dangerous drug and may cause changes in any of the bodily systems, but particularly the skin, liver, peripheral nerves, central nervous system and circulatory system. Certain effects of chronic arsenic poisoning tend to subside, but others do not. Simple irritation of the gastrointestinal, respiratory and genitourinary tracts usually disappears shortly after use of the medicine has been discontinued. Lesions of the skin, liver and blood vessels, however, do not regress in many instances. Goodman and Gilman[4] have stated that large quantities of arsenic are excreted through the kidneys up to 70 days after the last dose has been taken. After that, excretion is usually minimal, although considerable amounts of arsenic can

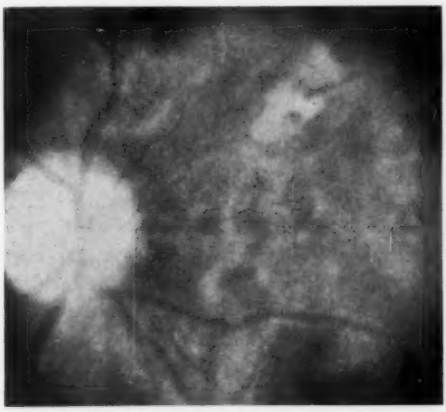


Fig. 2 (Prickman, Hollenhorst and Ammermann). Right eye. Aneurysm partially filled with clot and surrounded by transudate.

still be demonstrated, even years afterward, in the patient's hair and nails. We found arsenic in our patient's hair (10.2 mg. per 100 gm.) six years after arsenic therapy had been discontinued. None was found in his nail clippings at the same time. When involved, the skin shows typical pigmentation and hyperkeratosis of the soles and palms, as noted in our patient. Less frequent findings include itching, mild urticaria, maculopapular edematous eruptions, atrophic changes and sometimes squamous-cell carcinoma.

Hematologic reactions from arsenic include depression or, less frequently, hyperreaction of the bone marrow. Rare instances of agranulocytosis have been seen.[8, 9] Hemorrhagic encephalopathy with very serious loss of vision has been reported after the ingestion of Fowler's solution given as a treatment for asthma.[10] Inorganic arsenic is known to cause retrobulbar neuritis with central scotomas, and tryparsamide therapy is apt to result in extreme contraction of the peripheral fields and even in blindness.

Of special interest in relation to the case reported is the effect of arsenic on the vascular system. Arsenic is one of the most potent capillary poisons, in acute arsenic poisoning causing extreme dilatation and later arteriolar damage, especially in the vessels in the splanchnic area, but also in the extremities.

In 1898, Geyer[11] described gangrene in patients who drank water contaminated by arsenic, and Butzengeiger has reported a series including six cases of gangrene of the toes or fingers, 15 of milder circulatory disturbances, and seven of acrodermatitis atrophicans that occurred under similar circumstances. In the few instances in which histologic examinations were made in the latter series, the findings were not uniform but changes were found similar to those seen in arteriosclerosis and in endarteritis obliterans. Arteriosclerosis as a cause of the changes was excluded by age, since most of his patients were between 30 and 40 years and one was 17 years of age. The author concluded that the known ingestion of arsenic was the most reasonable explanation for the changes encountered.

In the early literature on chronic arsenic poisoning, the results of ophthalmoscopic examinations are rarely mentioned, so that it is questionable in many instances whether the retina was examined or not. Of special interest is the large series of patients in whom de Haas[12] found what he considered to be significant arsenuria. Many of his patients had edematous areas in the retina, and some had very small hemorrhages in the peripapillary region. Three of these patients had taken Fowler's solution. Four patients had retinal hemorrhages, and one appeared to have retinitis proliferans.

Terrien[13] called attention to various toxic manifestations reported to have followed the injection of arsphenamine, including conjunctival and corneal hyperemia, sclerokeratitis, iritis, myopia, cataract, optic neuritis, and hemorrhage into the vitreous. Morpurgo[14] reported hemorrhage into each macula following a single injection of arsphenamine.

Scheinker[15] discussed arsphenamine encephalopathy and described distention and engorgement of the veins, stasis of blood in the capillaries, degeneration and necrosis of the vessel walls, and hemorrhage into the tissue.

The vascular changes observed in the retina of our patient did not resemble those observed in individuals with diabetes mellitus, except that microaneurysms were present at the ends of a few venules. The pathologic changes at the first examination were those of a rather typical toxic retinopathy. Later, dilation and neovascularization developed on the venous side of the capillary system. Hemorrhage occurred from portions of these abnormal structures on at least two occasions. The arterioles appeared normal.

Recent studies by Michaelson[16] and by Wise[17] have indicated that the stimulus to formation of microaneurysms and new ves-

sels in the retina is supplied by a substance elaborated in the presence of hypoxia of the retina and obstruction to venous return flow. In the present case, the retinal hypoxia may have resulted from capillary stasis, as suggested by the dilated capillaries observed at the first examination, or from direct damage to the retinal tissues themselves. Probably, the involvement of the veins was secondary rather than primary.

It is of interest that another patient, a man with proved arsenical peripheral neuritis, was found to have considerable sheathing of the retinal veins resembling the perivenous sheathing described by Rucker[18] under the term, "retinopathy of multiple sclerosis." It is possible that the sheathing noted could have represented an early stage of the retinitis proliferans that developed in our patient.

The long-continued administration of arsenic, its demonstrated presence in the body six years after arsenic therapy for asthma was stopped, evidence of its toxic effects in the skin, and the lack of further progression of the ocular disease in our patient all argue strongly for the possibility that the retinopathy was secondary to chronic arsenic poisoning.

Chronic infection

Our patient had chronic bronchitis and chronic purulent sinusitis for a long time during which the retinitis proliferans was increasing in severity. Chronic bronchitis in association with chronic sinusitis is commonly encountered in our clinic, but not in association with retinopathy. Focal infection in a patient with diabetes is known to stimulate the development of early retinitis proliferans. The role of infection in producing the retinopathy in this case, either by itself or in association with arsenism or latent diabetes, is unknown.

Diabetes mellitus

The retinopathy found in our patient is not of the type seen in association with diabetes, although capillary microaneurysms were present. The retinitis proliferans of diabetes usually appears late in the course of the disease, comes predominantly in patients with juvenile onset of the disease, and is characterized by lesions that almost always are on or near the optic discs. The major pathologic changes in the retinas of our patient were in the midperiphery or far periphery, as is very characteristic of Eales' disease. These changes preceded by six years the appearance of diabetes, which may well have been induced by steroid therapy of asthma. Certain conditions associated with diabetes mellitus have been shown, however, to precede clinical diabetes by several years. For example, necrobiosis lipoidica diabeticorum may appear from one to five years before the symptoms of diabetes develop. Also, it is well known that unusually large babies have been born to apparently nondiabetic women who in later years become diabetic.

Diabetic retinopathy, however, is not generally recognized as one of the conditions that precede clinical diabetes by several years. Also, curiously, control of diabetes mellitus does not seem to benefit the diabetic retinopathy.

New vessel formation like that observed in our patient is a rare phenomenon except among diabetics. It occurs in conditions in which some degree of retinal hypoxia is present; for example, with retinal-vein obstruction, retinal periphlebitis, hemorrhagic glaucoma, and retrolental fibroplasia. There is an overgrowth of capillaries, not only into the retina, but up into the vitreous itself. Since there is lack of tissue support for these new capillaries, and since they have only a thin endothelial wall, they tend to rupture readily and to cause hemorrhage into the vitreous. Any exertion is likely to break them, and it is a common experience for such ruptures to occur during lifting, trauma or hypoglycemic shock.

The occurrence of fragile veins and capillaries with or without microaneurysms in the fundi of the eyes, regardless of cause,

is particularly hazardous in patients with asthma, inasmuch as many of them are given to hard overcoughing. Not infrequently, such patients cough hard enough to break a rib and occasionally produce emphysema of the mediastinum and subcutaneous tissues. It is extremely important in such instances to control the asthma thoroughly by avoiding any factors that precipitate coughing such as smoke, fumes, dust, exertion, sudden temperature changes, and colds. Complications such as sinusitis, bronchostenosis, or bacterial infections of the air passages should be corrected or treated vigorously. Antibiotics should be used when indicated. Symptomatic remedies for the relief of bronchospasm should be used promptly and in adequate dosage to avoid bronchospasm and hard coughing. No measure likely to relieve the patient, with the exception of arsenic therapy, should be overlooked.

Summary

Bilateral retinopathy with microaneurysms and vascular proliferation, possibly as a toxic manifestation of arsenism, developed in a patient with known asthmatic bronchitis. Later, as a result of overcoughing in association with asthma, rupture of a retinal capillary occurred, leading to hemorrhage into the vitreous with impairment of the vision. Other manifestations of arsenism and general measures for control of asthma are discussed, along with the additional possibility that either infection or preclinical diabetes mellitus caused the toxic retinopathy in this case.

Mayo Clinic.

References

1. Sollmann, T.: A Manual of Pharmacology: And Its Applications to Therapeutics and Toxicology. Philadelphia, Saunders, 1957, ed. 4.
2. Pliny the Elder: Natural History. (Translated by W. H. S. Jones.) Loeb Classical History, vol. 6. Cambridge, Harvard Univ. Press, 1952, p. 55.
3. Gay, F. S., and Gay, E. D.: The Gay treatment of asthma. Mississippi Doctor, **29**:142-144 (Nov.) 1951.
4. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology, and Therapeutics for Physicians and Medical Students. New York, Macmillan, 1955, ed. 2.
5. Hansen-Pruss, O. C.: Arsenic in the treatment of asthma. Ann. Allergy, **13**:1-14 (Jan.-Feb.) 1955.
6. Butzengeiger, K. H.: Ueber die chronische Arsenvergiftung: I. Ekg-Veränderungen und andere Erscheinungen am Herzen und Gefässsystem; II Schleimhautsymptome und Pathogenese. Deutsch. Arch. klin. Med., **194**:1-16 (Jan.) 1949.
7. Roth, F.: Ueber die Spatfolgen des chronischen Arsenismus der Moselwinzer. Deutsch. med. Wchnschr., **82**:211-217 (Feb.) 1957.
8. Eagle, H., and Magnuson, H. J.: The systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2, 3-dimercaptopropanol (BAL). Am. J. Syph., **30**:420-441 (Sept.) 1946.
9. Gattner, M.: Medikamentöse Arsenvergiftung mit Fowlerscher Lösung. Ztschr. ges. inn. Med., **8**: 233-236 (Mar. 1) 1953.
10. Prickman, L. E., and Millikan, C. H.: Hemorrhagic encephalopathy during arsenic therapy for asthma. J.A.M.A., **152**:1711-1713 (Aug. 29) 1953.
11. Geyer, L.: Ueber die chronischen Hautveränderungen beim Arsenicismus und Betrachtungen über die Massenerkrankungen in Reichenstein in Schlesien. Arch. Dermat. & Syph. **43**:221-280, 1898.
12. de Haas, H. K.: Ueber Erkrankungen der Netzhaut und des Sehnerven durch Arsenikvergiftung. Arch. f. Ophth., **99**:16-57, 1919.
13. Terrien, F.: Des complications oculaires après emploi des arsénobenzols. Arch. ophtal., **46**:513-534 (Sept.) 1929.
14. Morpurgo, F.: Ueber einen Fall von Netzhautblutungen nach Kalomel-Salvarsanbehandlung. München. med. Wchnschr., **61**:657 (Mar. 24) 1914.
15. Scheinker, I. M.: Genesis of encephalopathy due to arsphenamine (central vasoparalysis due to arsphenamine). Arch. Path., **37**:91-98 (Feb.) 1944.
16. Michaelson, I. C.: The mode of development of the vascular system of the retina: With some observations on its significance for certain retinal diseases. Tr. Ophth. Soc. U. Kingdom, **68**:137-179, 1948.
17. Wise, G. N.: Retinal neovascularization. Tr. Am. Ophth. Soc., **54**:729-826, 1956.
18. Rucker, C. W.: Retinopathy of multiple sclerosis. Tr. Am. Ophth. Soc., **45**:564-570, 1947.

TOBACCO AMBLYOPIA*

The evolution and natural history of a "tobaccogenic" disease

H. Silvette, Ph.D., H. B. Haag, M.D., and P. S. Larson, Ph.D.
Richmond, Virginia

In many ways, the subject of tobacco (or nicotine) amblyopia is one of the most interesting and, when viewed in an historic light, one of the most revealing of the so-called tobaccogenic diseases; for it illustrates, as none other of these diseases so well does, the phenomenon of "birth, growth, and senescence" of a disorder which, it seems, may at best have been largely illusory. Tobacco amblyopia (including tobacco-alcohol amblyopia) is thus an object lesson in the natural history of tobaccogenic disease, which the physician interested in medical history may wish to keep in mind when the question of tobacco etiology is raised in other diseases as fashionable now as tobacco amblyopia once was.

Tobacco amblyopia was first described by George Joseph Beer in 1792 and later in 1817; it was noticed again by Mackenzie in 1835. (A more lengthy historic account of tobacco and alcohol amblyopia has been given by Hirschberg, 1879.) Grouping the number of subsequently published papers on tobacco or tobacco-alcohol amblyopia by decades, we have succeeded in finding only 13 articles printed between 1861 and 1870.

In the years 1871-1880, there appeared 16 papers; in 1881-1890, the relatively large number of 54; in 1891-1900, 21; in 1901-1910, 35; in 1911-1920, 15; in 1921-1930, 36; in 1931-1940, 33; in 1941-1950, 20; and in 1951 and later, 14 papers—to which we must add an annotation which appeared in the *British Medical Journal* (1:1582, 1959) after our review had been completed and which promptly called forth a rash of correspondence in those pages. This latter phenomenon appears to indicate that it is not a simple lack of interest in tobacco amblyopia which has been responsible for the descending slope of the publication frequency curve, but rather a genuine paucity of publishable material.

It is to be further remarked that the number of cases of tobacco or tobacco-alcohol amblyopia reported in these publications follows much the same pattern of distribution in time and also shows a peak in the decade 1881-1890. Out of 935 cases appearing in the examined literature from 1861 to the present time, 480 or over 50 percent were reported between 1871 and 1890. In reflecting upon this apparent decline in the number of cases of tobacco amblyopia, what immediately strikes the mind is that the time-curve of tobacco consumption has, on the contrary, continued steadily upward; this conspicuous lack of parallelism between disease incidence and tobacco consumption—a positive parallelism between which has been accorded, in the case of the alleged smoking-lung cancer relationship, a certain degree of etiologic significance by several recent authors—affords an opportunity for productive speculation.

Assuming that the incidence of a disease has apparently gone down while exposure to its presumed etiologic agent has significantly risen, several possible explanations suggest themselves. The most obvious is that the presumed relationship is not causative. There is also the possibility that the organ-

* From the Department of Pharmacology, Medical College of Virginia. This study was supported by a grant from the Tobacco Industry Research Committee. We also wish to acknowledge the kind assistance of the Library of the American Tobacco Company Research Laboratory for obtaining for our review many of the articles cited in foreign publications. The material presented has been largely excerpted from a manuscript of a monograph currently in preparation in which the authors deal comprehensively with the world literature on all aspects, experimental and clinical, of the biologic effects of tobacco.

ism has developed in time some resistance to the causative agent, either hereditarily determined or as a result of external factors (for example, better general health and nutrition). Genetically determined changes in resistance may be ruled out, since but one century is less than a moment in human evolution. Nor can one avoid the suspicion (now unprovable) that many of the earlier reported cases of tobacco or tobacco-alcohol amblyopia had been falsely diagnosed, which leads to the not unwarranted belief that later ophthalmologists, confronted with a dim-sighted patient, did not end their diagnostic search and etiologic analysis as soon as it had been ascertained that the patient smoked. The only alternative to this latter explanation is the rather cynical conclusion that tobacco amblyopia is just as common today as it was in 1881-1890, but that cases of it are so old-hat by now that the physician-author no longer feels their publication will advance either medicine or his own career.

Fortunately the great mass of published material on tobacco amblyopia contains within itself sufficient inconsistencies and contradictions to enable one to cancel out a good deal of it. This rather tedious labor is justified, not by the isolated importance of tobacco amblyopia alone (as the relatively small space allotted to this once notorious disease in modern textbooks will confirm), but rather because, as we have said, a full account of the rise and fall of tobacco amblyopia as a prototype of "tobaccogenic disease" is not without contemporary significance.

It is still true of tobaccogenic disease in general, as Lewis (1901) remarked of this disorder in particular, almost in the heyday of tobacco amblyopia, that among the enormous number of smokers only a very small proportion become amblyopic and this proportion would be still further reduced if it were possible to exclude nontobacco complicating factors.

The key question was again posed by Heaton, McCormick and Freeman (1958) more than one-half century later: Why should only a few people who smoke get this amblyopia? Whatever the answer to this crucial question, it is difficult to believe that tobacco or tobacco smoking comprises any significant part of it.

Definition

By definition of tobacco amblyopia, as Heaton, McCormick and Freeman (1958) have pointed out, tobacco is a necessary factor; that is, it is not possible for nonusers of tobacco to develop *tobacco* amblyopia.

Now, such a definition as previously stated has the great merit of avoiding the uncomfortable fact that nontobacco users may, and sometimes do, come down with a disease identical (so far as one can tell) to that suffered by tobacco users; and if authors in the currently fashionable field of lung cancer would only make use of this same qualification, the dispute over a specific (for example, tobacco) causation in this particular disease would evaporate into the fog of atomized distinctions. Thus, male-rural-cigarette-lung-cancer, by definition, could develop only in cigarette smoking farmers; noncigarette lung cancer, only in nonsmokers and so forth, through all combinations and permutations of "etiologic factors" suggested for this disease. Simple introduction of *X* into the several definitions would provide for any etiologic factor or factors so far unknown or unrecognized.

L. J. Lautenbach (1898b) employed the term "tobacco amblyopia" to express a bilateral retrobulbar neuritis of the optic nerve with central color scotoma, followed later by atrophy of the optic nerve, occurring in one addicted to the excessive use of tobacco and not, so far as known, using any other toxic agent to excess. Although Samelsohn (1882) considered as incorrect the strict distinction between toxic amblyopia and retrobulbar neuritis, both Uhthoff (1886, 1887) and Groenouw (1892) regarded the two afflictions as different diseases, in spite of the seemingly identical anatomic findings.

According to Uhthoff, the clinical picture of retrobulbar neuritis is distinguished from that of toxic amblyopia by the extent and kind of scotoma; only very few cases of toxic amblyopia were said to resemble retrobulbar neuritis in their field of vision findings, and vice versa. Apparently, "retrobulbar neuritis" is itself a nebulous term (Bussy, cited in Lancet, **2**:818-819, 1926).

Ruata (1925), among others, considered nicotine amblyopia as one of the numerous symptoms of chronic tabagism, a symptom which was never primary but always preceded or was accompanied by other difficulties, such as, cardiovascular, digestive, and nervous disorders. Nicotine amblyopia disclosed an advanced and relatively grave state of intoxication by tobacco.

Most authors distinguish between blindness and amblyopia; almost a century ago, Hart (1863a) stated it was time to discard the word amaurosis, that the term had originated in the dark ages of ophthalmic science, and had been well defined as describing a condition in which the patient saw nothing and the surgeon just a little.

The term "smoker's eye" apparently has been recently coined as a synonym of tobacco amblyopia. A Chester, England, court was told that heavy smoking may cause a driver to confuse the color of traffic signals. The defendant had driven through a traffic light, believing that the signal was green and in his favor and a specialist diagnosed the defendant's condition as "smoker's eye" (Lancet, **2**:411, 1958). This popular description of a condition occurring in smokers but not peculiar to them is rather dangerously misleading, as are lay interpretations of technical medical publications.

In connection with the latter, the antitobacco publicist Roy Norr (Hearings before a Congressional Sub-Committee, 1957, p. 272) has rhetorically demanded:

"How many thousands have been crushed into a pulp due to sudden failure of sight suffered by a hard smoking driver due to nicotine amblyopia causing a sudden spasm of the blood vessels of the eye? How many mysterious air disasters have occurred because the pilot's vision and depth perception have been affected by smoking? It is only recently that aviation doctors have taken steps to warn pilots of the danger. Medical literature is full of papers on that subject."

Medical readers will hereinafter be able to interpret them for themselves.

Incidence

One must clearly distinguish between (1) the incidence of tobacco amblyopia among all users of tobacco, and (2) the incidence of smoking and other tobacco use among sufferers from amblyopia, that is, the incidence of tobacco amblyopia in all cases of toxic amblyopia whatever the origin.

1. It is the impression of many students of this disease that the incidence of tobacco amblyopia in the tobacco-using population is low (Lewis, 1901; Lillie, 1934; Greeves, 1936; Heaton et al., 1958; among others), and decreasing (Orr, 1936; Lancet, **1**:1009-1010, 1938), although Vandegrift (1914) and Hedges (1957) held that tobacco amblyopia was more common than suspected.

2. The difficulty of ascertaining the true incidence of tobacco amblyopia among patients with eye disease is enhanced by the habit of many authors of reporting cases of "tobacco-alcohol amblyopia" without distinguishing between the relative importance or unimportance of the "nicotine" or the "alcohol" factor.

Combining extensive series of eye cases reported in the literature, we have calculated that, of a total of 287,869 eye patients, 2,492 or approximately 0.86 percent were diagnosed as having cases of tobacco-alcohol amblyopia (based on Horner, 1878; Galezowski, 1883b, 1884; Éperon, 1890; Galezowski, quoted by Ramsay, 1895; Finlay, 1901; Voigt, 1906; Scholtz, 1907; Bachstez, 1920; Bachstez and Purtscher, 1920; Lindner, 1920; de Andrade, 1923; Cossu, 1923; de Vincentiis, 1927). According to a later authority, tobacco-alcohol amblyopia was seen

in about 0.3 to 0.5 percent of all patients newly admitted to the eye clinic of the Massachusetts Eye and Ear Infirmary (Carroll, 1935a).

Summarizing a representative collection of extensive series in which tobacco amblyopia was distinguished from tobacco-alcohol amblyopia, the incidence rate of presumably pure tobacco amblyopia was calculated to be 0.77 percent in a total of 228,339 patients with eye disease (based on Chisolm, 1878; Galezowski, 1883b, 1884; Finlay, 1901; Voigt, 1906; Bachstez, 1920; Bachstez and Purtscher, 1920; Pick, 1920; Meyerhof, 1921; Hanke, 1920; Traquair, 1927, 1928, 1931). In the absence of detailed case histories and knowledge of the authors' criteria of what constituted tobacco and/or alcohol use, it is difficult to evaluate these statistics. Furthermore, it should be pointed out, that the incidence rate of presumably pure tobacco amblyopia is very heavily weighted by the very large number of patients—136,157—in Traquair's series, and his reported incidence rate of 1.12 percent.

Several authors have presented statistics pointing to an increase in the incidence of tobacco amblyopia during wartime, particularly in countries suffering from food scarcities; this was observed during and immediately after World War I (Jendralski, 1922; Sattler, 1923; Bachstez, 1920; Bachstez and Purtscher, 1920; Traquair, 1931; Gjessing, 1939) and for World War II (Hambresin and Schepens, 1946). There appears little doubt that the increase in tobacco amblyopia during both World Wars was due to nutritional factors, rather than to any change in the degree or manner of tobacco use (see later in text).

Factors affecting the incidence of tobacco amblyopia

Early observers noted that their cases of toxic amblyopia were all in men (Horner, 1878; Nelson, 1880), and it has been commonly stated and/or observed that tobacco amblyopia usually occurs in men (Lyle, 1905; Dowling, 1908, 1909; Greeves, 1936; Heaton et al., 1958; among others) and is very rare in women (Eales, 1887; Gunn, 1887; H. Eales, 1890; Lyle, 1905; Scholtz, 1907; Cossu, 1923; Traquair, 1927, 1928, 1931; Usher, 1927). However, Uhthoff (1911) warned that one should not assume a special predisposition of men, since women are also attacked when sufficiently exposed. It is statistically unfortunate that cases of tobacco amblyopia are now so relatively rare that the sex incidence of the condition cannot be determined in these years when women, too, are "sufficiently exposed."

As to the age incidence, virtually all authorities are agreed that tobacco amblyopia is most frequent in middle-aged men, approximately between the ages of 40 and 60 years (Nelson, 1880; Ramsay, 1895; Kerr, 1901; Lyle, 1905; Bär, 1906; Scholtz, 1907; Dowling, 1908, 1909; Gy, 1913; Cossu, 1923; Usher, 1927; Traquair, 1931; Lillie, 1934; Greeves, 1936; Hambresin and Schepens, 1946; Heaton et al., 1958; among others).

Tobacco amblyopia is said to be rare before the age of 30 years (Groenouw, 1892), although patients have been reported in their early 20's (Kerr, 1901; Scholtz, 1907; Traquair, 1931) and even in their teens (Bär, 1906; Usher, 1927). Lautenbach (1898b) believed tobacco amblyopia to be more prevalent among young people than commonly supposed.

At the other extreme, the incidence of the disease was said to drop after the age of 60 years (Groenouw, 1892), though tobacco amblyopia has been reported in patients 80 years of age and older (Kerr, 1901; Scholtz, 1907; Traquair, 1931; Heaton et al., 1958). (In a group of men over the age of 60 years, no relation was found by F. Edwards, McKeown and Whitfield [1959] between smoking habits and defective vision.)

From his examination of Negro tobacco-workers, Dowling (1908) was inclined to conclude that this race enjoyed an immunity to tobacco blindness. Confirmation or dis-

proof of this belief has apparently not appeared in the literature.

During 15 years of experience in Turkey and the Levant, Van Millingen (1888) never met with a single instance of tobacco or alcohol amblyopia in a native-born Turk, and in 11 years' practice in Egypt, Meyerhof (1921) found no cases of tobacco amblyopia in native-born Egyptians. This latter author commented that native-born young Egyptians were accustomed to use a huge amount of tobacco, mostly in the form of cigarettes, but alcohol was completely avoided by the Mohammedan Egyptian—and probably also by the Mohammedan Turk.

Lopez (1900) reported that tobacco amblyopia was an exceptional occurrence in Cuba, probably because its tobacco was superior in quality to that of other countries, and possesed a lower nicotine content. However, Finlay (1901) was enabled by his personal medical practice in that country to contradict authoritative statements to the effect that Cubans and Spaniards were immune to tobacco amblyopia. Van der Hoeve (1927) stated that he had never seen cases of tobacco amblyopia in Holland, and did not believe it ever occurred there, though he did not know why.

It has been noted that the incidence of the disease is highest in those occupations which gave the most opportunity for smoking while at work (Groenouw, 1892; Scholtz, 1907). It is interesting to note that many authorities have reported that tobacco amblyopia is absent or rare and exceptional in tobacco workers (Ely, 1880; Shears, 1884; Snell, 1894a, b; Gy, 1913; Meyerhof, 1921; Volokonenko, 1925; Neuschueler, 1928; among others), the condition when found being ascribable to excessive personal use of tobacco by the individual rather than to the working conditions (Dowling, 1892, 1908, 1909).

According to Kretschmer (1942), however, tobacco amblyopia was a special consequence of industrial poisoning to which young women tobacco employees were particularly sensitive. Dowling (1908, 1909), on the other hand, stated that women cigar-workers seemed to be practically exempt from toxic amblyopia.

Relationship to kind and degree of tobacco use

It appears to be agreed that prolonged exposure to tobacco is necessary to produce a toxic amblyopia (Sichel, 1863a, b, c, 1864; Chisolm, 1878, 1887; Galezowski, 1883a, b, 1884; Nettleship, 1887; Ramsay, 1895; Heaton et al., 1958; Brit. M. J. 1:1582, 1959; Doggart, 1959). Chisolm (1887) had never seen tobacco amblyopia from tobacco use of less than 10 years and all but one of the patients of Heaton, McCormick and Freeman (1958) had smoked for 30 years and more. In the latter series, the remaining patient had smoked for only 1.5 years. Nettleship (1887) reported two cases in which onset of the disease followed one and three years of smoking, respectively.

For the most part, authors have felt that the absolute amount of tobacco used was not a determining factor, although some (for example, Galezowski, 1883a, b, 1884; de Vincentiis, 1927) have related the disease to immoderate use of tobacco. Wordsworth (1863b) remarked that he would not expect to find loss of visual function in all old abusers of tobacco any more than he would expect to find cirrhosis in all old sots. Loureiro (1865) stated that the amount of tobacco which would lead to harmful consequences to individuals in sound condition could not be specified.

In fact, the occurrence of tobacco amblyopia bears no direct relation to the quantity of tobacco consumed (Lewis, 1901). The amount of tobacco smoked by patients with this disease varies (Heaton et al., 1958) and the condition is not necessarily caused by the consumption of large quantities of tobacco (Greeves, 1936). In certain idiosyncracies, however, tobacco absorbed even in small quantities, such as in smoke-filled rooms, can provoke visual troubles (Galezowski,

1883a, b, 1884). But these latter are transient, whereas true tobacco amblyopia is not.

Several authors have given their estimate or calculation of the amount of tobacco necessary to produce toxic amblyopia (assuming sufficient length of time of exposure); the weekly consumption varied from 0.5 to 9.0 oz., and an average might be struck at about 3.0 to 4.0 oz. (Sichel, 1863a, b, c, 1864; Eales, 1887; Nettleship, 1887; Kerr, 1901; Traquair, 1931). According to Groenouw (1892), up to 0.5 oz. of tobacco was probably harmless.

Elderton (1927) statistically analyzed Usher's (1927) data on 1,100 cases of tobacco amblyopia and found that the amount of smoking for the development of this condition varied considerably with the individual; there was as much variability in the amounts smoked by the patients as there was in the amounts smoked by the men in a control series of 500 pipe smokers without visual impairment.

Men who were 50 years of age or over when they were found to have tobacco amblyopia were, on the average, smoking the same amount of tobacco as the men of the same age in the control series; men who were under 50 years of age when they developed the disease were smoking more tobacco than the men in the control series; men who developed the defect before they were 30 years of age were smoking about 1.0 oz. more tobacco a week than men in the control series; men who developed amblyopia between 35 and 40 years of age were smoking about 0.5 oz. more. It appears then, that differences in tobacco consumption were not as determinative as individual "sensitivity" or "predisposition."

It has been suggested that tobacco amblyopia may result from the use of strong and/or coarse tobaccos (Eales, 1887; Ramsay, 1895; Kerr, 1901; Adrogue, 1923), such as a shag type (Brit. M. J., 1:1582, 1959). According to Terrien (1908), visual disturbances depend on the manner of use of tobacco and its nicotine content but, according to Elderton's (1927) analysis of Usher's (1927) data, the strength of the tobacco, as judged by the amount of nicotine, did not seem to be of importance; the patients were found to be smoking the stronger types of tobacco in the same proportion as the general public and there was no conclusive evidence that those smoking the stronger tobaccos developed amblyopia at an earlier age.

Groenouw (1892) stated that all of the usual forms of using tobacco may lead to toxic amblyopia; Lautenbach (1898a) was convinced that tobacco must be smoked to produce the disorder; and most authors have, in fact, implicated smoking more than other forms of tobacco use. Chisolm (1887) stated he had never seen a case of amblyopia due to the use of snuff, and Gy (1913) agreed that the condition was rare in snuff takers, although it may occur (Doggart, 1959).

In 1887, Chisolm remarked that he had never seen a case of amblyopia due to the use of chewing-tobacco, but in 1890, he reported two cases in men who chewed tobacco. Ramsay (1895) never saw a case of tobacco amblyopia in a patient who chewed but did not smoke and Lautenbach (1898a) was so convinced that tobacco must be smoked to produce amblyopia that he permitted tobacco chewing during treatment of this condition. Other authors have noted that amblyopia was rare in tobacco-chewers (Gy, 1913, Meyerhof, 1921); still others, that some or many amblyopia patients may chew (Kerr, 1901; Pick, 1920; Doggart, 1959).

It has often been said that tobacco amblyopia shows a preference for cigar smokers (Gy, 1913; Meyerhof, 1921; among others). Chisolm (1887) reported having seen tobacco amblyopia caused by as little as one-half cigar a day, although Groenouw (1892) felt that up to three cigars a day were probably innocuous. Lillie (1934) thought tobacco amblyopia most common in patients who smoked cigars or pipes excessively and, in Hedges' (1955) experience, all patients with far-advanced amblyopia had been cigar smokers.

On the other hand, Greeves (1936) stated

that amblyopia only occasionally resulted from cigar smoking; and Heaton, McCormick and Freeman (1958) stated that cigars are seldom responsible for this disease. These latter authors stated that tobacco amblyopia usually affects persons who smoke strong pipe tobacco; and pipe smoking has been considered by others the commonest cause of the disorder (Greeves, 1936; Leishman, 1951; Brit. M. J., 1:1582, 1959; Doggart, 1959).

With respect to cigarette smoking, Lillie (1934) stated he had never seen a case of nicotine amblyopia from this cause; and recently, the statement was made that there is no record of cigarette smoking causing the disease (Brit. M. J., 1:1582, 1959); but this latter pronouncement was promptly questioned by writers who had themselves seen cases in cigarette smokers (A. T. G. Evans, 1959; Cohen, 1959; Smith, 1959; Heaton et al., 1959) or who were cognizant that the literature contained such cases (Ewing, 1959; Heaton et al., 1959).

It appears to be true, nevertheless, that cigarettes are seldom responsible for tobacco amblyopia (Traquair, 1931; Greeves, 1936; Heaton et al., 1958, 1959)—or, a less common cause than pipes (Doggart, 1959). Perhaps, then, the great change to the cigarette in smoking habits following World War I is at least partially responsible for the marked drop in reported tobacco amblyopia in recent decades.

A possible explanation of the different incidence rates of tobacco amblyopia in pipe and cigarette smoking has been suggested by Leishman (1951), who related them to possibly different routes of absorption of nicotine: in the former manner of smoking, it was deemed likely that the nicotine was swallowed, causing a slow upset of gastric function, with resulting metabolic derangement, which in turn might produce the lesions of tobacco amblyopia. The *British Medical Journal* (1:1582, 1959) also considered that perhaps the difference was related to the fact that cigarette smoking is mainly an inhalation into the bronchi and lungs, whereas pipe smoking is often accompanied by much swallowing into the stomach.

Relationship to alcohol consumption

De Vincentiis (1927) has described the debate which has come down through the years on the relative importance of alcohol and tobacco in the production of toxic amblyopia. It will be sufficient at this date to indicate the general suggested relationships, since (as will appear) neither tobacco nor alcohol seems to be of true etiologic significance. Presumably, teetotalling smokers show "pure" tobacco amblyopia; nonsmoking drinkers, a "pure" alcohol amblyopia; while individuals who both smoke and drink may develop tobacco-alcohol amblyopia. Thus, the differentiation depends upon retrospective case histories; and the distinction is further rendered difficult in that, as Lewis (1901) pointed out, alcohol alone will produce a condition of the optic nerves very similar to that which is ascribed to tobacco.

In brief, the following relationships between tobacco and alcohol in the production of toxic tobacco-alcohol amblyopia have been suggested or maintained by the several authorities:

1. Both alcohol and tobacco are causative agents (Horner, 1878; Martin, quoted in Brit. M. J., 1:744, 1879; among others).

2. Either agent alone is capable of causing the disease (Terrien, 1908; Gy, 1913; among others), although usually and most frequently free indulgence in alcohol is associated with heavy smoking (Treitel, 1879; Ramsay, 1895; Kerr, 1901; Parsons, 1901c; H. W. Lyle, 1905; Terrien, 1908; Gy, 1913; de Andrade, 1923; Peters, 1926; deSchweinitz, 1927; D. J. Lyle, 1947; Crain, 1958; Brit. M. J., 1:1582, 1959).

3. The influence of alcohol in the production of tobacco-alcohol amblyopia is secondary or doubtful (Traquair, 1927, 1928, 1931), since tobacco-alcohol amblyopia is observed in nondrinkers (Berry, 1882; Elderton, 1927; Hambresin and Schepens, 1946) but not in nonsmokers (Gunn, 1887; Morton, 1887; Nettleship, 1887), and is gener-

ally connected with excessive smoking but not with alcoholism (Groenouw, 1892; Scholtz, 1907; Ruata, 1925; Rivet, 1948). Furthermore, tobacco-alcohol amblyopia improves when smoking is stopped, even though the patient continues to drink (Berry, 1882, 1887; Nettleship, 1887; P. J. Evans, 1939).

4. Alcohol indirectly favors the toxic effects of tobacco on the eye (Berry, 1887; Gunn, 1887; Nettleship, 1887; Heaton et al., 1958). However, some persons with amblyopia have been reported to derive temporary benefit from alcohol, as regards their vision (Gunn, 1887).

5. The influence of tobacco is minor, the etiologic factor in toxic retrobulbar neuritis being practically always alcohol and very often both alcohol and tobacco, but rarely if ever tobacco alone (Bussy, cited in Lancet 2:818-819, 1926). Moreover, the condition is seen in patients who do not use tobacco (von Fellenberg, 1918), and improves when drinking is stopped, even though smoking is not curtailed (Lautenbach, 1886).

From the previous statement, it appears likely that no generalization may be made which is valid in any particular case. Carroll (1935a) believed that increased susceptibility of the patient was a far more important factor than the amount of tobacco or alcohol consumed. As a rule, neither tobacco nor alcohol directly affects the eyes, unless the substances have first attacked the general health (Krimsky, 1936a, b), a view which may be taken as a rather obscure expression of the current belief that nutritional retrobulbar neuritis is a true deficiency disease (D. F. Moore, Lancet **2**:527, 1958).

There is only historic interest in the earlier view of Horner (1878), Sachs (1888), and deSchweinitz and Edsall (1903a, b), which has been discussed by deSchweinitz (1922), that intestinal toxins elaborated from gastrointestinal catarrh caused by the abuse of alcohol and tobacco had a greater effect in creating toxic amblyopias than either the alcohol or tobacco itself, although this vaguely foreshadowed the current concept of an indirect influence of these substances.

Uhthoff (1886, 1887) classified 204 cases of so-called retrobulbar neuritis as to etiology: 64 were due to alcohol, 45 to alcohol and tobacco, 23 to tobacco alone, giving a ratio of 3:2:1. The remaining cases were either of unknown or nontobacco-alcohol etiology.

Role of tobacco

Wordsworth (1863a) stated that all classic writers attributed to tobacco its full share of causation as a source of amaurosis. Hutchinson (1863) analyzed a collection of cases of cerebral amaurosis and, while he saw great difficulty in the way of belief in a tobacco etiology, he considered there was enough clinical suspicion to insist on the disuse of tobacco in all potential cases of this disease. Loureiro (1865) observed no single instance of cerebral amblyopia or amaurosis in which tobacco alone was responsible.

It is apparent that such statements have no real value as evidence so far as the etiology of "tobacco amblyopia" is concerned. The opinions of later writers (for example, Nettleship, 1879; Browne, 1888a; Lautenbach, 1898b; Gutierrez-Muro, 1934; Gottlieb, 1941, 1942; Hedges, 1955; Brit. M. J., 1:1582, 1959; Doggart, 1959) that tobacco is a cause of toxic amblyopia (but not necessarily the only agent capable of producing this condition) are also not synonymous with proof, although the observation that recovery from tobacco amblyopia may lie in mere abstinence from tobacco (Hirschberg, 1879; Berry, 1882; among others) would seem to implicate tobacco in some cases. Elderton (1927) concluded that there was no evidence that excessive smoking in itself would cause tobacco amblyopia.

Lokshima (1936) raised the question of whether toxic diseases of the optic nerve might be caused by the methanol content of tobacco smoke but this appears unlikely. P. J. Evans (1939) believed the primary etiologic factor in tobacco amblyopia to be a

toxic agent, derived possibly by a process of fermentation and present in higher amounts in the heavier and darker tobaccos.

According to Leishman (1951):

> Opinion has recently favoured some noxious agent associated with tobacco as the ultimate source of (tobacco amblyopia), since it has not been possible to connect the symptoms with the toxic actions of nicotine. While it is therefore unlikely that tobacco amblyopia is a direct result of the action of blood-borne nicotine on the visual mechanism, it is still possible that the condition may be an indirect result of nicotine poisoning.

Hambresin and Schepens (1946) had also considered that tobacco amblyopia was only one symptom of chronic tobaccoism. Lautenbach (1898b) believed tobacco amblyopia to be induced, not by the direct absorption of nicotine but by the volatile products of combustion. However, if it be true that tobacco amblyopia is found in tobacco chewers and snuff takers, this cannot invariably be the case.

According to Traquair (1931), the occurrence of tobacco amblyopia is an excellent illustration of the relationship of the true cause and the exciting cause. The true cause is tobacco, but the disease is determined in many instances by a depression in the patient's health. It is equally in accord with the clinical facts to maintain that it is tobacco which is the exciting cause, and that the true cause is the patient's "ill health" or, as expressed today, the patient's nutritional deficiency in vitamins. Thus, in persons with even mild vitamin-B_{12} deficiency, the retina or optic nerve is unduly sensitive to tobacco (Heaton et al., 1958).

Nontobacco factors in tobacco amblyopia

Since it has been obvious to all observers that a majority of tobacco users, even those not in perfect health, do not develop tobacco amblyopia, several authors have postulated an individual hypersusceptibility to tobacco in those patients who have developed the disease (Hutchinson, 1873; Terrien, 1908; Traquair, 1931; among others). Eales (1887), also noting that the disease is comparatively rare although the smoking habit is common, believed there was probably an inherited tendency to it.

General ill health or loss of health was said to predispose the individual to tobacco amblyopia (Loureiro, 1865; Eales, 1887, 1890; Lewis, 1901; Traquair, 1931; Krimsky, 1936a, b). Various debilitating conditions or "nervous exhaustion" may be included in this category (Loureiro, 1865; Berry, 1884; Browne, 1888a; Kerr, 1901; Lyle, 1905; Terrien, 1908; Hambresin and Schepens, 1946). Psychic shocks have also been mentioned as precipitating causes of the disease (Traquair, 1927, 1928; Hambresin and Schepens, 1946).

Several diseases have been specifically mentioned as predisposing the sufferer to toxic (tobacco-alcohol) amblyopia: digestive disorders (Loureiro, 1865; deSchweinitz and Edsall, 1903a, b; Dunn, 1910); diabetes (Nettleship and Edmunds, 1882-1883; Edmunds and Nettleship, 1883; Browne, 1888a; Moore, 1888; Terrien, 1908; deSchweinitz and Fewell, 1926; Shannon and McAndrews, 1934; Carroll, 1956; Crain, 1958; Doggart, 1959); syphilis (Terrien, 1908; Bussy, cited in Lancet, **2**:818-819, 1926).

Many authors have pointed out that malnutrition (starvation, loss of weight, undernourishment, and so forth) seems to increase the patient's susceptibility to tobacco amblyopia (Berry, 1884; Eales, 1887; Browne, 1888a; Lyle, 1905; Cramer, cited by Bachstez, 1920; Binet and Crosnier, 1945; Hambresin and Schepens, 1946; Crain, 1958; Doggart, 1959; among others). By the same token, Lindner (1920) believed that the very low incidence of retrobulbar neuritis found by him in Lublin was due to the good nutritional status of these patients.

The nutritional disturbance responsible for this increased susceptibility to toxic amblyopia appears to be a vitamin deficiency, although Carroll (1937, 1943, 1944, 1945) did not consider tobacco-alcohol amblyopia purely the result of a deficiency state: if it were, one might expect to find a type of am-

blyopia indistinguishable from tobacco-alcohol amblyopia among patients who did not smoke or drink but who had deficiency conditions such as pellagra. Carroll suggested that patients suffering from subclinical nutritional deficiency might have a markedly increased susceptibility to tobacco and alcohol, the tobacco producing a toxic action on malnourished cells. He added that it appeared likely that people consuming, absorbing, and utilizing normal amounts of vitamin B never develop tobacco amblyopia.

Other authors have also emphasized the etiologic factor of vitamin-B deficiency in optic neuritis of tobacco or alcohol habitués (Duggan, 1937; Cushman, 1939; Gottlieb, 1941, 1942; Maxwell, 1953; among others), but clinical trials have not convincingly shown that it is a deficiency of vitamin-B complex which is the cause of tobacco amblyopia (Heaton et al., 1958). Smoking had been stopped in many instances which improved most cases, and often the diet and drinking habits of the patients had been simultaneously altered.

Leishman (1951) found that tobacco amblyopia and the amblyopia of pernicious anemia may co-exist in the same subject more frequently than might occur by chance. In view of the fact that two of the 14 patients with tobacco amblyopia studied by Heaton, McCormick and Freeman (1958), and 10 of 75 cases reviewed by Leishman (1951), were found to have pernicious anemia, the former authors reviewed the published cases of retrobulbar neuritis in pernicious anemia, and stated that a survey of these case reports suggested that many of these patients with pernicious anemia could be described as having tobacco amblyopia.

In addition, in retrobulbar neuritis of pernicious anemia, the histologic findings in the optic nerves (Bickel, Arch. Psychist. Ber., **53**:1106, 1914) appear to be similar to those observed in tobacco amblyopia (Duke-Elder, cited by Heaton et al., 1958). Thus, tobacco amblyopia and the retrobulbar neuritis of Addisonian pernicious anemia may be one and the same condition (Heaton et al., 1958).

Diagnosis of tobacco amblyopia

Early writers gave most prominence to (1) rapid failure of sight with no ophthalmoscopic or other obvious external changes to account for the loss of vision (Shears, 1884; Hartridge, 1886), and (2) a central scotoma for colors (Leber, 1869; Griffith, 1886; Hartridge, 1886; Eales, 1887). According to Krimsky (1934), tobacco amblyopia consists of a definite symptom complex the pathognomonic sign of which is a central scotoma and enlargement of the blindspot.

Hambresin and Schepens (1946) considered the sign of the nasal letter particularly characteristic, as noted by Traquair (1931); when the patient reaches the last line he is capable of perceiving on the visual scale, he distinguishes poorly the letter he fixes but clearly recognizes the letter on the nasal side of the letter fixed. Hambresin and Schepens emphasized the importance of determining the field of vision in studying tobacco amblyopia.

The criteria on which Heaton, McCormick and Freeman (1958) based the diagnosis of tobacco amblyopia in their patients were as follows: (1) the patient must be a smoker; (2) a centrocaecal scotoma must be present; (3) this scotoma must be horizontally oval with a sloping edge and most readily detected by a reduced stimulus, that is, with a red or a small white test object; (4) the scotoma must be bilateral, though not necessarily equal on the two sides; (5) the defect for color must exceed that for white; (6) there must be definite nuclei within that scotoma on the horizontal meridian; (7) the impairment of the temporal color field must exist within the 30-degree circle (in the more advanced cases, a similar defect is also seen to a small light test object).

The recent annotator in the *British Medical Journal* (1:1582, 1959) stated that the diagnosis of tobacco amblyopia is not easy,

and went on to outline it; careful case history is the first prerequisite. The occurrence of progressive failure of central vision in an elderly man without any evidence of significant intraocular disease is highly suggestive of tobacco amblyopia. The appearance of optic atrophy is seldom seen in the early stages and is purely a terminal phenomenon. The presence of a centrocaecal scotoma in the visual field, particularly to red and green objects, is diagnostic of the condition.

Differential diagnosis of tobacco amblyopia

Some authors have maintained that so-called tobacco amblyopia has no distinctive characteristics which would enable even an experienced physician to distinguish this condition from several other kinds of retinitis or retrobulbar or optic neuritis (Meany, 1908; Percival, 1925; Lillie, 1934). Others have held that retrobulbar neuritis is a different disease from tobacco amblyopia, and have given rules for the differential diagnosis between the two (for example, Groenouw, 1892; deSchweinitz and Fewell, 1926).

In particular, some have believed that tobacco amblyopia could not be separated from alcohol amblyopia (Uhthoff, 1911; Neuschueler, 1928). Others (for example, Martin, quoted in Brit. M. J., 1:744, 1879) distinguished the signs and symptoms of amblyopia caused by alcoholic poisoning from those resulting from abuse of nicotine. The response to cessation of smoking was said by Lawford (1890) to be indicative in the differential diagnosis of tobacco amblyopia, in that abstinence from tobacco leads to improvement.

Powers (1886) believed the use of amylnitrite to be of great assistance in the differential diagnosis of this condition. In his experience, no benefit was derived from the administration of this drug in progressive atrophy from other causes, while in tobacco amblyopia, vision was immediately and markedly improved.

Carroll (1935a) discussed the importance of distinguishing the findings in tobacco amblyopia in aged patients from those of senile macular degeneration. Hambresin and Schepens (1949) discussed the differential diagnosis of tobacco amblyopia and heredofamilial optic atrophy.

Signs and symptoms of tobacco amblyopia

The literature contains a number of graphic descriptions of the typical sufferer from tobacco amblyopia and, in view of the seeming likelihood that some contemporary physicians may not encounter such patients in their own practice, the descriptions are given here in detail.

According to Groenouw (1892), the typical cases of toxic amblyopia are presented by men of middle age who are heavy smokers and are also usually addicted to the enjoyment of alcoholic beverages. The general condition is disturbed; lack of appetite, insomnia, constipation, diminution of sexual desire, and a feeling of fatigue and depression are very rarely absent. Sometimes it is only possible for the patient to count fingers at a distance of a few meters; complete blindness is never present.

According to Ramsay (1895), those affected with nicotine amblyopia usually present a strong healthy appearance unless suffering from debility rising from some other cause. They rarely admit ill health, but questioning brings out that for some time before the dimness of vision was first observed, they had been worried and sleepless, and suffered from loss of appetite and digestive disturbances. The typical appearance of one suffering from tobacco amblyopia was described by Dunn (1910) as follows:

> The middle-aged patient walks boldly into the out-patient room, acts as if he saw plainly, and neither in gait nor in gesture displays the loss of vision which is present in his case. The burden of his complaint is that he is losing his sight. While making his statements, however, we noticed the pallor of his face, the tremulousness of his hands, the furring on the dorsum of his tongue as is apparent when he is told to show it. To test for the

tremors, direct the patient to stretch out his arms straight from the shoulders, the hands approximating but not touching the thumbs. The eyes showing no signs of external disease, we next proceed to ask him some questions, from his replies to which we ascertain the following details. That everything for about the past three months has appeared to be "in a fog," as he expressses it; that he can only read large print; that the sight is now so bad that he has been compelled to cease his employment; that for some time he had felt "shaky"; that he has no appetite for his breakfast; that he has great difficulty in distinguishing between the colour of gold and silver; that he has sleepless nights; and that he has particularly noticed that everyone he meets looks ill, their faces being the colour of yellow wax. Next we inquire as to his habits. He admits that he smokes from a quarter of an ounce to half an ounce of shag daily; that he has done so for many years; that directly he rises in the morning he begins to smoke, and continues doing so, off and on, while at work until his mid-day meal.

As described by Traquair (1931), the patient is usually a man of about 50 years, who states that his sight has been failing for a few weeks or several months. Almost at once the observer notices the smell of stale tobacco. (Doyne [1889] reported that patients with tobacco amblyopia had a peculiar "dry and fusty" smell; and a note by the editor at the end of Doyne's article stated he had also observed this.) There may be tremor of the hands. When asked to describe his visual failure, the patient sometimes says he cannot read a newspaper, more often that he cannot recognize the faces of his friends in the street; this statement is one of several which are characteristic. Vision is usually said to be a little better in the dusk than in bright daylight and the patient complains of a silvery mist between him and anything he looks at. These symptoms have usually come on gradually and without any exciting cause but it is not uncommon to find that the visual failure has been preceded by an illness, an accident, or even a purely psychic disturbance.

Ophthalmoscopic findings

In general and in the majority of cases, there appear to be little or no characteristic ophthalmoscopic findings in tobacco amblyopia (Sichel, 1863a, 1865a, b; Loureiro, 1865; Edmunds and Nettleship, 1883; Shears, 1884; Connor, 1890; Traquair, 1931; Lillie, 1934; Carroll, 1935a, Hambresin and Schepens, 1946; among others), although sometimes pallor of the temporal half or quadrant of the optic disc has been observed (Leber, 1869; Hirschberg, 1879; Shears, 1884; Groenouw, 1892; Voigt, 1906; Dowling, 1908; Traquair, 1931; Carroll, 1935a; among others).

Berry (1882), however, put little trust in the ophthalmoscopic finding of paleness of the temporal half of the disc. Pallor of the entire papilla, and not only of the temporal half, has been reported (Uhthoff, 1880; Gunn, 1887), especially in extremely chronic cases (Lillie, 1934). In cases of early tobacco amblyopia, it has sometimes been observed that the papillas were hyperemic rather than pale (Shears, 1884; Bernheimer, 1901; Bär, 1906; Dowling, 1908). In none of Shears' (1884) 40 cases was any sign of atrophy of the optic disc found but, according to Dowling (1908), atrophy of the disc finally takes place.

Although the optic discs may show no change at any time during the course of the disease, a definite pallor of the temporal side of the disc in the area occupied by fibers of the papillomacular bundle was noted by Carroll (1935a) in 19 of 55 patients with tobacco-alcohol amblyopia. Once this pallor became manifest, it never disappeared, although the patient's vision and fields became normal. The degree of pallor did not necessarily bear any relation to the visual acuity or the visual fields.

Pupils

Martin (quoted by Brit. M. J., 1:744, 1879) concluded that one of the characteristic signs of tobacco amblyopia was constriction of the pupils, which are dilated in alcoholic amblyopia. Other writers have also reported more or less persistent and marked miosis (Galezowski, 1883b, 1884; Éperon, 1890; Dowling, 1892, 1908; Rodiet and Cans, 1906).

According to Éperon (1890), absence of the pupillary reflex was one of the less frequently observed signs of tobacco and alcohol amblyopia. Dorrell (1913) found that the dilatation of the pupil obtained when the skin of any part of the body was electrically stimulated was either in abeyance or obtained only by increased strength of stimuli in tobacco amblyopia. However, this test was not specific for tobacco poisoning alone, since similar results were obtained in spinal-cord disease.

Visual acuity

Diminution of visual acuity is one of the characteristic signs of tobacco amblyopia (Galezowski, 1883b, 1884), and this observation has been frequently recorded (Horner, 1878; Voigt, 1906; Terrien, 1908; among many others). However much the acuteness of central vision may be lowered in tobacco amblyopia, the patient shows no difficulty or awkwardness in walking about (Nelson, 1880), and has not the "amaurotic aspect" so common in subjects of progressive atrophy of the nerves (Nettleship, 1879). Carroll's (1935a) patients usually had trouble reading but were able to perform household duties or manual labor without difficulty.

In cases of nicotine and alcohol amblyopia, the ratio of visual acuity for the normal eye over that for the diseased eye was found by Foerster (1871) to be 1/5 (the light sensitivity ratio was 1/1). The visual acuity ratio reported by other authors was about 1/10 (Nelson, 1880); between 5/200 and 20/30 (Groenouw, 1892); and 20/200 or worse (Carroll, 1935a). However, some patients had 20/20 vision in each eye, and this was considered important by Carroll, since patients with good visual acuity do sometimes complain of marked blurring of vision due to the scotomas. Groenouw (1892) found only a loose connection between the dimensions of the defect for red and white and the acuteness of vision.

According to Bär (1906), visual acuity varied within wide limits, depending upon whether the scotoma was absolute or only relative. Tests for light sensitivity gave a diminution in all cases of absolute scotoma and frequently in the case of relative scotoma. There was conspicuous disproportion between distant vision which was almost normal in most cases, and close vision which showed pronounced deterioration. Traquair (1931) also often found a great discrepancy between distant and near vision, the distant vision being relatively better. On the other hand, Hutchinson (1887), pointing out some exceptions to the usual findings in tobacco amblyopia, reported one case in which good near vision was retained throughout, with great defect of distant vision and other typical symptoms.

As long as the scotoma has not attacked the fixation point, the vision remains good in tobacco amblyopia; when the fixation point is affected, the decrease of the acuity is sometimes very rapid (Hambresin and Schepens, 1946). Since there is no parallel between visual acuity and the importance of the alterations of the visual field, the measure of the acuity is an inadequate test for judging the gravity or evolution of a tobacco amblyopia.

Location of the visual defects

In tobacco amblyopia, central vision is said to be affected, though the peripheral vision may remain good (Lyle, 1905) and Poulard (1908) stated that this was a constant and infallible symptom of toxic amblyopia. However, Harman (1904) declared that the commonly held view, that in tobacco amblyopia vision was only affected centrally, was not true; that it was also diminished peripherally when a sufficiently delicate test was used, that is, mapping in dim light, and perhaps diminished also over the entire field. Salva (1897) concluded that, if the intoxication lasted long enough, the peripheral bundles as well as the macular bundle could degenerate.

Harman (1904) and Voigt (1906) noted that amblyopia patients showed a narrowing of the field of vision. Carroll and Ireland

(1935) regarded toxic amblyopia as being of an island type, that is, an island of decreased vision in an otherwise normal field. According to Schrumf-Pierron (1927), chronic tobacco poisoning may give rise to hemianopsia.

The bilateral nature of the visual defects in tobacco amblyopia has been pointed out by many observers (Horner, 1878; Nettleship, 1879, 1887; Nelson, 1880; Groenouw, 1892; Ramsay, 1895; Lautenbach, 1898b; Lyle, 1905; Dowling, 1908; Terrien, 1908). However, exceptions to this are not very uncommon and illustrative cases in which the eyes were unequally affected have been reported (Hutchinson, 1887; Morton, 1887; Nettleship, 1887; Eales, 1887). Apparently the disease "begins" unilaterally at any rate (Guelliot, 1877; Eales, 1887; Traquair, 1927, 1928, 1931).

Examination of visual acuity in extensive series of cases of tobacco-alcohol amblyopia has shown that the disease does not always affect both eyes equally (Scholtz, 1907; Cossu, 1923). Cossu (1923) has pointed out that, in other eye diseases as well as in amblyopia, the tendency also exists for the left eye to be more susceptible than the right eye.

Day and night vision

According to the majority of observers, sight in tobacco amblyopia is better in the evening or in a dim or subdued light, than in the daytime or in sunshine or bright light (Hirschler, 1871; Horner, 1878; Nettleship, 1879; Nelson, 1880; Groenouw, 1892; Harman, 1904; Bär, 1906; Terrien, 1908; Dowling, 1908; Traquair, 1931; Carroll, 1935a). Others, however, found that their patients did not see as well at night as during the daytime (Guelliot, 1877; Martin, quoted by Brit. M. J., 1:744, 1879). According to Hirschler (1871), the statement of many patients that they can see better during the evening than during the day applies only to larger objects, but not to reading; this is due to the fact that the "glittering haze" or "glimmering mist" which covers all objects is removed with twilight, and as a result the contours become sharper. This "fog" or "mist" or "haze" between the amblyopia patient and anything he views has often been described (Dowling; Traquair; Carroll; among others).

Scotoma

A central scotoma for colors (usually red and green) is generally found in tobacco or tobacco-alcohol amblyopia (Leber, 1869; Horner, 1878; Galezowski, 1883b, 1884; Lawford, 1883; Connor, 1890; Hedges, 1957; among many others). The central scotoma in tobacco amblyopia is only defective (amblyopic), never blind (amaurotic); it is a "relative," not an "absolute" scotoma (Nettleship, 1879). Not all amblyopic patients have showed this defect, however (Hirschler, 1871; Frost, 1887; Voigt, 1906), and cases have been reported of monocular central amblyopia (Uhthoff, 1887; Doyne, 1889; among others).

Uhthoff (1887) always found a central scotoma in toxic amblyopia; in most cases the defect existed only for red and green, rarely for blue. Morton (1887) saw one case of central scotoma for blue, as well as for red and green. Hutchinson (1887) stated it was fairly common for the field for yellow to reveal a central scotoma, as well as red and green. He had one case in which yellow and green alone were affected. Greenwood is cited as having seen a case with a field for blue also showing a central scotoma. Hutchinson had also seen one case where there was a central scotoma for white as well as for colors.

In a series of 55 cases of tobacco-alcohol amblyopia reported by Carroll (1935a), centrocaecal scotomas were noted, usually much larger for red than for blue. Apparently, however, all workers did not always test their amblyopia patients with colors other than red and green, or even with more than red, so that it is difficult to tell whether the defects in color vision found in isolated cases represent the exceptions or the rule.

Although evident enough for white, the central scotoma in tobacco amblyopia is especially apparent for those colors which are perceived only in the central part of the field, and especially for red and green (Nettleship, 1879). Central vision for green is affected first, for red later, and for blue last (Lyle, 1905). As in the relative scotoma, the sensitivity for green likewise suffers most during regression of the disease and sensitivity to green reappears only toward the end (Bär, 1906). Sensitivity for red suffers next most severely. In connection with the central absolute scotoma, white is sometimes perceived as blue, especially during regression of the disease.

Hirschberg (1879) considered that a pericentral scotoma was characteristic of alcohol amblyopia, and a paracentral one of tobacco amblyopia. Hirschberg's view was emphatically contested by Treitel (1879), and Uhthoff (1887) stated that he could not confirm it. Both a patient with uncomplicated tobacco amblyopia and one with uncomplicated alcohol amblyopia, had similar types of scotoma, according to Carroll and Franklin (1936).

Most authors have described the scotoma as more or less paracentral (Nettleship, 1879; Nelson, 1880; Groenouw, 1892; H. W. Lyle, 1905; Bär, 1906; Doyne, 1922; among others). Traquair (1931) emphasized that the scotoma is not central, but centrocecal; the macular fibers are not the most severely involved. The scotoma develops by extension from the nasal side of the blindspot, is very uniform in character, and such variations as it exhibits are usually within narrow limits. In this way, it was said to differ from the multiform scotomas of multiple sclerosis, Leber's disease, and other conditions. Traquair maintained that no other form of scotoma is produced by tobacco. Other writers have also noted that ovoid centrocecal scotomas were more or less characteristic of tobacco-alcohol amblyopia (Hambresin and Schepens, 1946).

In general, according to Hambresin and Schepens, (1946), the scotoma has two nuclei, each composed of a small darker zone with margins which shade off; one is near the blindspot and is the first to appear and the other appears later and is found next to the fixation point. Such absolute scotomas frequently presented no coherent surface, being separated by the bridgelike zone of a relative scotoma (Bär, 1906). During regression of the symptoms, the absolute scotoma generally completely disappeared first, a relative scotoma disappearing only considerably afterward.

Doyne (1922) described three types of scotomas met with in tobacco amblyopia: (1) a large scotoma involving the blindspot and the area between the blindspot and fixation, but which stopped just short of the actual fixation point; (2) a scotoma lying close to fixation within the five-degree circle connected by a relative area to the blindspot, which may or may not be prolonged toward fixation; (3) a scotomatous finger pointing from the blindspot toward fixation. This author rated the first as the most severe, and the third as the least severe. The size of the absolute scotoma, however, had no certain relation to the visual acuity. (In connection with this latter observation, it may be remarked that Vandegrift [1914] described a case history to illustrate his contention that the scotoma begins before any loss of vision develops.)

P. J. Evans (1939) found the following distribution of position of maximum density of scotomas: confluent with blindspot, 71; halfway between blindspot and fixation point, 18; between fixation point and halfway, six; between blindspot and halfway, four; maximum central, eight.

Nelson (1880), like Traquair (1931) later, believed the scotoma originated at the blindspot and extended toward the fixation point. He based this belief on: (1) the gradual failure of sight, for if the scotoma began at the fixation point, central vision would probably become at once so bad as to oblige the patient to seek medical advice;

(2) the shape of the scotoma; (3) its density; (4) its manner of receding; (5) the fact that the fixation point is free in certain cases. The scotoma was invariably denser at and toward the blindspot than at the fixation point.

Good descriptions of the dynamic changes occurring in the scotomas in tobacco amblyopia have been given by Groenouw (1892) and Duggan (1935), to which the interested reader is referred. It should be noted, however, that a sufficient number of case reports indicate that such "ideal" descriptions as that of Groenouw have their exceptions.

Color differentiation in tobacco amblyopia

Guélliot (1877) reported six cases of "nicotinic amaurosis" in which colors were never confused. However, according to Hirschler (1871), amblyopic patients do not see objects in their true color, they can distinguish blue for the longest time. H. W. Lyle (1905) noted that color vision was so affected that gold and silver coins were often mistaken one for the other—a disability unfortunately, no longer of practical importance!

Voigt (1906) found that 15 of 16 amblyopia patients showed uncertainty in recognizing and differentiating colors. The principal colors confounded were: red confounded with pink, dark brown, or black; green, with light blue or white (Dowling, 1908). Only central color perception was affected. The colors in the periphery could be distinguished without much difficulty. Red was especially difficult for Carroll's (1935a) patients with tobacco-alcohol amblyopia to see —which might or might not constitute a legal defense for driving through a red stoplight.

Galezowski (1883b, 1884) reported the occurrence of chromatopsias and chromatic phenomena in tobacco amblyopia; Terrien (1908) reported dyscromatopsia. Subjective color disturbances in tobacco-alcohol amblyopia were said to have occurred especially in the case of more intelligent patients (Bär, 1906).

Herbolsheimer (1942) is authority for the statement that acquired color-blindness may be caused by alcohol or tobacco, or the two in combination. Groenouw (1892) pointed out that the defective color vision in tobacco amblyopia differed from congenital color-blindness in several ways, including a considerable reduction in the acuteness of vision.

Laboratory findings in tobacco amblyopia

Carroll (1935b) reported that the cerebrospinal fluid in 10 cases of tobacco-alcohol amblyopia was essentially normal, except that the total protein content tended to be elevated. The highest protein levels were found in two patients who had not yet decreased their intake of tobacco and alcohol.

DeSchweinitz and Edsall (1903a, b) studied blood, urine, feces, and some stomach contents of seven patients with tobacco-alcohol amblyopia and reported evidence of a marked disturbance of digestion or metabolism, or both. Brognoli and Citterio (1951) carried out numerous clinical and laboratory tests for hepatic function on 24 patients with nicotine-alcohol amblyopia, and reported that notable symptoms of hypofunction of the liver frequently existed. In two of the patients studied by Heaton, McCormick and Freeman (1958) (see later in text), abnormal liver function tests were recorded.

In 15 cases of tobacco amblyopia tested by Leishman (1951) with a gruel meal, free acid was never present in samples taken during the first hour, nine subjects gave an achlorhydric response to histamine, five gave a poor or normal response, and only one gave a hyperchlorhydric response. Leishman stated that acid deficiency is thought to occur in about 25 percent of the normal population and, on this basis, his figures were said to be significant.

In a study of 13 patients with tobacco amblyopia, the vitamin-B_{12} levels in the serum

were significantly lower on the average (less than 50 percent) than those of healthy controls (Heaton et al., 1958). In two patients, tobacco amblyopia and neurologic features suggesting vitamin-B_{12} deficiency were associated with free acid in the gastric juice, abnormal liver function tests, and low serum-B_{12} levels.

Retinal arteries and retinal pressure

A comparatively well-marked diminution in the caliber of the retinal arteries has been reported in cases of tobacco amblyopia (Buxton, 1888; Connor, 1890). Kruger (1911) described cases of tobacco-alcohol amblyopia in which various retinal arterial vascular changes could be demonstrated, and Doggart (1959) thought it not inconceivable that changes in the retinal vessels can result from the use of tobacco. Kruger raised the question of whether the vessels were not frequently primarily diseased, and, in a certain proportion of the cases, the retina first suffered in tobacco-alcohol amblyopia. However, in a series of 55 patients with tobacco-alcohol or tobacco amblyopia, Carroll (1935a) found the number of patients showing retinal angiosclerosis to be no more than might be expected from any equally large group of patients with the same age distribution.

According to Bidault (1936), retinal pressure was normal in 25 percent of 40 patients with nicotine-alcohol amblyopia, decreased in 50 percent and increased in only 25 percent. The increases were in patients under 45 years of age. Thus, amblyopic patients tended to have a relative retinal arterial hypotension. Orzelesi (1938) also found a relative retinal hypotension in the majority of his patients with nicotine-alcohol amblyopia, while the remaining patients presented normal ratios (retinal pressure/brachial pressure).

Contrary to popular opinion, smoking actually does not seem to produce vasoconstriction in a majority of subjects and may in some persons increase the intraocular blood supply rather than decrease it. In experiments carried out by Bettman, Fellows and Chao (1958), cigarette smoking constricted the retinal blood vessels in a few humans, changed them not at all in most, and actually dilated them on rare occasions.

Histopathology of tobacco amblyopia

This section may be prefaced with the comment by Percival (1925) that those who have worked at the pathology of the condition found in tobacco amblyopia gave very different accounts of what they had seen; which reminds one of the tongue-in-cheek question asked the young doctor who might be thinking of specializing in pathology: "Can you say the same thing in twenty different ways?" ("How to become a specialist," Middlesex Hosp. J., February, 1959).

Pathologic changes in tobacco or tobacco-alcohol amblyopia have been thought to involve either the circulatory or the nervous elements of the eye, or both; although, in actual examination, it is exceptional to find such changes in this condition (D. J. Lyle, 1947). In three cases of tobacco amblyopia, the histopathologic findings have been reported in great detail (Samelsohn, 1882; Sachs, 1888; Birch-Hirschfeld, 1901), although, in the light of such comments as those by Percival and Lyle, it is questionable whether such detailed findings have any general validity. The curious case of "white atrophy of the optic nerves" also makes one cautious in accepting the results of earlier pathologic studies.

Wordsworth (1863a) reported three cases of apparently pure tobacco amblyopia and stated that only one pathologic condition was seen, namely, that of white atrophy of the optic nerves. He added that, in all his cases, he recognized this condition in a greater or lesser degree. Hart (1863a) took exception to this view, and said he had been unable to trace the connection with tobacco in any case of white atrophy which had come under his notice; moreover, white atrophy is found

in children and females and male nonsmokers. Wordsworth (1863b) replied that if Hart would continue to examine cases, he would soon be convinced that tobacco was largely concerned in the production of amaurosis and that the change in the nervous structures of the eye was ultimately one of atrophy. Hart (1863b) remained unconvinced.

Treitel (1879) also claimed to have observed atrophy of the optic nerve as the termination of several cases of toxic amblyopia, although he himself admitted that in these cases he might perhaps have been confronted by a complication of toxic amblyopia with genuine atrophy; he located the seat of the disease in the optic nerve. Hirschberg (1879) considered it not proven that abuse of tobacco often leads to progressive atrophy of the optic nerve; and Hartridge (1886) stated that, in his experience, optic atrophy had never resulted. Thereafter, optic nerve atrophy seems to have disappeared from the tobacco amblyopia literature.

Groenouw (1892) considered three possibilities for the site of the pathologic process in toxic amblyopia: either the process attacks, directly or indirectly, the light-perceptive elements (retina), or it attacks the nerve fibers specializing in conducting the light perception (optic nerve, chiasma, or optic tract), or else, finally, it has its seat in the central organs (cerebral cortex).

Concerning the latter mechanism, Lautenbach (1898b), maintaining that tobacco amblyopia is always bilateral, deduced from this that the primary effect of tobacco was not on the axial fibers of the optic nerve but on a central cerebral inhibiting center governing these axial fibers. However, Lautenbach's premise is not valid, for there are authentic reported cases of monocular amblyopia and no other author has suggested a central cause for this condition.

Nelson (1880) subscribed to the theory of Leber (1869) that the basic cause of tobacco amblyopia was a retrobulbar neuritis confined to certain fibers which lie superficial and close to the temporal side of the sheath, and which simply bend over into the retina and run outward in a horizontal direction toward the macula. Many writers have considered that the picture in tobacco amblyopia is indistinguishable from that of retrobulbar neuritis while others have considered the two as separate diseases (see previous text). It has already been noted that the histologic findings in alcohol amblyopia, tobacco amblyopia and retrobulbar neuritis of pernicious anemia, appear to be similar.

Sachs (1888) considered that the generally valid anatomic basis of toxic amblyopia was the partial degeneration of the optic-nerve tract and degeneration of the papillomacular fasciculus. Nuel (1896) claimed that the central scotoma of toxic amblyopia was primarily a macular disease and not an interstitial neuritis. The primary lesion was of the nerve fibers on a greater or lesser scale; then immediately but secondarily, an overgrowth of interstitial connective tissue occurred, along with vascular changes in the portion of the nerve primarily affected (Nuel, 1902). Terrien (1908) stated that there was ultimately a partial decoloration of the papilla in tobacco amblyopia, almost always on the temporal side, due to atrophy of the maculopapillary bundle, and Lillie (1934) considered the idea that only the maculopapillary bundle of nerves is affected seemed best established clinically.

Groenouw (1892) favored the view that the primary site of tobacco amblyopia was to be found in the optic nerve, and not in the chiasm or optic tract. According to D. J. Lyle (1947), toxic amblyopias from exogenous poisons attack chiefly the subchiasmatic optic nerve.

Fisher (1901) made use of Langley's classic work on the effect of nicotine on ganglion cells as a basis to argue that the central amblyopia in nicotine poisoning was due to an interruption in the transmission of those impulses which have to pass through the ganglion cells upon which the alkaloid

acts. He instanced some histologic facts which, if this view was admitted, would enable one to explain more satisfactorily than hitherto why direct vision suffers out of all proportion to indirect vision in tobacco amblyopia. This ganglionic action of nicotine has also been recognized, at least in part, by other writers.

It appeared probable to Birch-Hirschfeld (1901) that the ganglion cells of the retina were affected before or at least simultaneously with the nerve fibers. His own histopathologic findings in a case of tobacco amblyopia were said to indicate a primary affection of the nervous apparatus in the optic nerve and retina. On the basis of known anatomic findings and the pharmacology of nicotine, Parsons (1901a, b, c) theorized that the action of nicotine in toxic amblyopia was in part paralytic upon the synapses of the cone fibers or of the cone bipolars, or of both.

H. W. Lyle (1905) believed that the pathology of tobacco amblyopia might be looked upon as a primary degeneration of the ganglion cells in the neighborhood of the macula lutea with a secondary degeneration of nerve fibers arising from these cells and involving the maculopapillary bundle. The interstitial changes noted were thought to be the accompaniment of the degenerative process in the optic nerve itself.

Wray (1905), arguing by very defective syllogism, pointed out that nicotine is used to paralyze ganglion cells; it is the ganglion cells which suffer in the retina in tobacco amblyopia, hence, nicotine is the cause of tobacco amblyopia. According to the annotator in the *British Medical Journal* (**1**:1582, 1959), the causal agent produces amblyopia by a direct action on the retinal ganglion cells.

Bussy (cited in *Lancet*, **2**:818-819, 1926), who questioned the accepted ideas of the pathology of the lesion of tobacco amblyopia, argued that if it were simply due to an inflammation of the interstitial tissue, neuroglia, and septa of the optic nerve leading to strangulation and atrophy of the nerve fibers, there would be no sound reason why it should select the macula for its manifestations rather than any other part of the eye. If, however, one admitted with Nuel (1896) that the primary lesion was in the ganglion cells of the macula and paramacula, that is to say, in the retina at the point of focus, the disease takes its place logically with scintillating scotomas and central amblyopias due to aspidium or quinine. Its apparent selectivity is due to the fact that the toxin renders cells of the ganglia capable of being decomposed by light, and the center, where most of the light is concentrated, is the first to go blind.

Samelsohn (1882) reported histopathologic observations on a patient and assumed as the primary cause of the entire condition a morbid proliferative process of the nerve at the optic foramen which, by compressing the optic nerve, induced circulatory disturbances and finally a descending neuritis. From their anatomic position, the papillomacular fibers at the optic foramen, where they enter the nerve stem, are those which are most abundantly supplied with blood due to the very fine capillary meshwork which surrounds them; consequently, according to Ramsay (1895), these fibers will be most liable to nutritional derangement when any toxic agent exercises an irritating action in their neighborhood.

Parsons (1901b, c) supposed the action of nicotine in toxic amblyopia to be in part vascular, causing vasoconstriction of the arterioles, which was said to explain the selection of the sparsely supplied macular region. Bussy (cited in *Lancet*, **2**:818-819, 1926), however, felt that no damage to the vascular system of the optic nerve could explain the lesion, since the connection between these vessels and the macula is not at all an intimate one.

Schieck (1903) postulated circulatory disturbances as the underlying cause of retrobulbar neuritis. He argued that the nerve fibers which maintain the retinal center were

most unfavorably situated as a result of their central course in the optic nerve in relation to nutritional disturbances in the optic nerve from vascular maladies or faulty quality of the blood. Thus, tobacco and alcohol were said to act on the nerve only by way of inducing a chronic nutritional disturbance of the vascular wall.

Dowling (1908) thought it probable that the changes observed in the papilla were caused by direct action of nicotine, causing contraction of the smooth muscle fiber and then diminishing the caliber of the minute blood vessels of the part. Irritation of the nerve tissue takes place at the same time, explaining the congested condition at the early stage of tobacco amblyopia. The pressure, and so forth, caused by the congestion finally produces a gradual atrophy of the disc and eventually portions of the contiguous retina.

Several writers have noted that the vision in tobacco amblyopia was improved by vasodilators and have considered that this supports the hypothesis that tobacco amblyopia is primarily due to the vascular spasm in the visual pathway (Powers, 1886; Cordes and Harrington, 1935; Duggan, 1937). Carroll (1937), however, challenged this idea; in many of his patients, the retinal vessels appeared normal and he had no success using sodium nitrite.

The Lancet (1:1009-1010, 1938), reviewed the origin of the theory that vascular spasm might be responsible for transient blindness from tobacco poisoning and the recent use of vasodilators in the treatment of tobacco amblyopia. It would appear that the lesion in nicotine amblyopia is primarily nervous rather than vascular (J. A. Gunn, 1930); and, although the factor of vasospasm cannot be excluded, it is probably not of very great importance except in the case of younger persons (P. J. Evans, 1939).

Farnarier (1928) reported that in certain smokers the first puffs of tobacco, if inhaled, caused at times the appearance of a central scotoma which was believed due to reflex angiospasm and he raised the question whether this phenomenon might play a role in the genesis of toxic amblyopia. Hambresin and Schepens (1946) suggested that tobacco amblyopia began with an enlargement of normal angioscotomas, particularly the centrocecal angioscotomas, which observation pointed to the retinal location of the lesion. The vessels in the centrocecal region carry the blood for the macular zone and the perivascular lymphatic spaces undoubtedly assure the evacuation of the tissue fluids.

If the cones must face metabolic difficulties, there will be alterations of the tissue fluids in which they are immersed. The congestion of the canals of perivascular evacuation would be shown in the visual field by an enlargement of the centrocecal angioscotomas resulting from an edema at the level of the retinal synapses. This could be the point of departure of a vicious cycle. The centrocecal region, inconvenienced by this poor circulation, would become less resistant to intoxication.

Neuschueler (1928) summed up the theories proposed to explain nicotine amblyopia as follows: (1) primary interstitial inflammation of the papillomaculary bundle, with predominating localizations in the optic canal and subsequent compressive action on the nerve fiber by the newly formed connective tissue (Uhthoff); (2) primary lesion of the vasal system, consisting in vasal neoformation and thickening of the walls, with phenomena of endarteritis (Schieck); (3) primary degeneration of the nerve fibers of the papillomaculary bundle, with secondary and simultaneous lesions of the ganglion cells in the macular region (Dalen); (4) primary lesion of the center of the retina, with secondary ascending degeneration of the papillomaculary bundle (Roenne).

Neuschueler did not consider any of these theories entirely satisfactory, especially since studies on the concomitant and predisposing causes are scarce, and little is known with regard to the individual factor. Having frequently noted radiographic signs of endocranial hypertension (possibly due to increase of secretion of the cephalorachidian

liquid on the part of the cerebral vessels, especially of the choroidal plexi), he believed that this hypertension, by compressing the optic nerves selectively and other cranial nerves eventually, might sometimes explain the pathogenic mechanism of nicotine-alcohol amblyopia.

Onset, course, prognosis, recovery

The onset of tobacco amblyopia has been described as sudden, rapid or abrupt (Bull, 1875; Horner, 1878; Shears, 1884; Filehne, 1885; Hartridge, 1886), or, on the other hand, as slow, gradual, or insidious (Ramsay, 1895; Kerr, 1901; H. W. Lyle, 1905; Terrien, 1905; Dowling, 1908; Vandegrift, 1914; Hambresin and Schepens, 1946). It is rather curious, though perhaps not very significant, that the earlier observers tended to emphasize the rapidity and the later observers the slowness of onset.

Carroll (1935a) stated that the onset was usually very gradual, but infrequently might be rather sudden. In the majority of the 26 cases of tobacco amblyopia reported by Nelson (1880), sight failed in two to six months and in a few cases, in two to six weeks; perhaps these figures may be taken to illustrate the two types of onset. It is interesting to note that in his own case (which may be taken to represent a minimum of both patient and observer error), Filehne (1885) stressed the sudden appearance of tobacco amblyopia in the midst of complete health.

According to some observers failure of sight in tobacco amblyopia progressed rapidly for a time and then remained somewhat stationary (Bull, 1875; Nettleship, 1887; Nettleship and Edmunds, 1882-83). Others, however, have described the course of the disease as progressive (Martin, quoted by Brit. M. J., 1:744, 1879; Kerr, 1901; H. W. Lyle, 1905; Dowling, 1908). Authors are in agreement that tobacco amblyopia never progresses to complete loss of sight (Hirschberg, 1879; Uhthoff, 1880, 1911; Berry, 1882; Traquair, 1927, 1928, 1931).

The prognosis in uncomplicated cases of tobacco amblyopia is generally favorable, especially if the patient gives up smoking and comes under early treatment (Ramsay, 1895; Terrien, 1908; Dowling, 1908). A hopeful prognosis should always be given (Traquair, 1931).

Berry (1887) found that recovery took place in all cases in which the vision was not much further reduced than to 20/200 and the scotoma did not reach to the inner side of the point of fixation when the tobacco had been stopped. When the vision was below 20/200 and the scotoma stretched to the inner side, or when some peripheral limitation of the visual field occurred, complete recovery did not occur. The absolute loss of green perception was considered by Treitel (1879) to be prognostically unfavorable in tobacco and alcohol amblyopia. In those cases of toxic amblyopia in which temporal optic atrophy is present, the prognosis was said by Duggan (1935) to be poor, although some improvement might be expected on treatment.

Griffith (1887) concluded from his study of 65 cases of tobacco amblyopia that there is a tendency for recovery to take place even without complete discontinuance of the toxic agent. However, recoveries under these circumstances are apt to be tedious and all speedy recoveries occurred in those who gave up tobacco completely.

Elderton (1927), following his statistical analysis of Usher's (1927) data on 1,100 cases of tobacco amblyopia, concluded that improvement in vision was difficult to measure but that the amount of tobacco smoked, the amount of alcohol taken before the patient was observed and the age of the patient, made practically no difference to the improvement effected. That recovery, or at least maintenance of useful vision occurs in spite of continued consumption of tobacco, shows that tolerance may be established (Traquair, 1931).

It is of interest to examine in some detail the relationship of recovery to tobacco consumption in two series of patients. Of the 65 cases of tobacco amblyopia studied by

Griffith (1887), 27 patients completely recovered their sight (of whom nine had almost entirely, and 18 had given up tobacco); 24 partially recovered their vision (of whom nine had reduced consumption of tobacco, 11 entirely stopped, and for four there was no record); 11 remained stationary (of whom two smoked as much as ever, one slightly reduced consumption, two greatly reduced; five entirely gave it up); three got worse (of whom two continued to smoke and one had given it up five to six years before reporting for observation).

In P. J. Evans' (1939) series of 55 cases, total recovery occurred in 23 patients (14 abstained, nine reduced consumption, none maintained consumption of tobacco); 27 showed partial recovery (six abstained, 20 reduced, one maintained consumption); five failed to recover (three maintained tobacco consumption).

Carroll (1943, 1944) found that patients on adequate diets made partial or complete recoveries in spite of their continued and unabated use of tobacco or alcohol or both, and the results were said to be at least as good as those obtained in any previous consecutive 25 patients (including those who abstained from the use of tobacco and alcohol while under treatment).

Summing up this aspect of the course of recovery: if the patient with tobacco amblyopia discontinues smoking, his vision usually improves but if he continues to smoke and takes large doses of vitamin B complex and a well-balanced diet, there will usually be improvement over a period of months in spite of smoking (Carroll, 1956).

The time required for recovery (presumably with the qualifications regarding tobacco use already mentioned), like the time of onset, has been variously described as in most instances rapid (for example, by Ruata, 1925), and always slow (for example, by Greeves, 1936). Recoveries were effected in two months or more (Berry, 1887); three to 42 months in about one-half of the patients (Griffith, 1887); in two to 10 (average five) months (Hambresin and Schepens, 1946).

When the patient ceases to use tobacco, the defect improves in about six weeks in mild or moderate cases and in two to three months in more severe cases. The improvement may continue slowly for several years to a certain point even though tobacco consumption has continued (Traquair, 1931). Riddell (1936) stated that recovery from tobacco amblyopia may take two years or longer—longer than is usually taught.

Commenting on the statement in the *British Medical Journal* (1:1582, 1959) that improvement in central vision should occur after a latent period of about four to six weeks after genuine cessation of any form of tobacco use, Stewart (1959) noted that the expected improvement, especially in the more elderly patient, may occasionally be protracted for as long as a year, yet with ultimate recovery of full normal visual acuity.

Filehne (1885) noted a four-week long exacerbation of his amblyopia despite complete abstinence from tobacco. Berry (1887) observed that recovery from tobacco amblyopia was often preceded by a time (three to six weeks) before any appreciable change took place and Traquair (1927, 1928, 1931) stated that an interesting feature of tobacco amblyopia was that vision sometimes became worse for a time after smoking had stopped.

M. Gunn (1887) wrote that he had not met with any instance of a second attack of toxic amblyopia. Berry (1887) noted that relapses were rare and Eales (1887) had never seen a recurrence of the disease. Nettleship (1887) saw only one case of relapse of amblyopia due to tobacco.

When recovery is established, moderate smoking is not injurious (Browne, 1888a), and, in many cases, tobacco has been smoked as freely as before the disease without provoking a recurrence (Morton, 1887). The low recurrence rate in tobacco amblyopia may possibly be due to the development of tolerance, as Traquair (1931) suggested, or may be due to better nutrition of the patient

under a physician's care, as seems likely in view of Carroll's (1943, 1944) work.

Treatment of tobacco amblyopia

Virtually all authors have considered abstinence from tobacco to be either necessary or important or desirable—it would not be useful to categorize the authors—in the successful treatment of tobacco amblyopia (Sichel, 1863a, 1865b; Loureiro, 1865; Hutchinson, 1873; Chisolm, 1878; Webster, 1880; Hartridge, 1886; Ray, 1887; Connor, 1890; Keyser, 1890; Noyes, 1890; Thompson, 1897; Finlay, 1901; Kerr, 1901; Galtier, 1902; H. W. Lyle, 1905; Bär, 1906; Dowling, 1908; Poulard, 1908; Hine, 1920; de Andrade, 1923; Carroll, 1935a; Hambresin and Schepens, 1946; Weekers, 1949; Saraux, 1954; Hedges, 1957; Crain, 1958; Brit. M. J. 1:1582, 1959; Doggart, 1959; among others).

In rare cases, tobacco amblyopia was not ameliorated by abstinence from smoking (Spicer, 1896; Galtier, 1902); in others, good recoveries were made in spite of continued smoking by the patients, especially following adequate vitamin therapy.

In many cases, abstinence from tobacco was supplemented by drugs (see later in text), or, more recently, by an enriched diet or vitamins. Regarding medication, Hambresin and Schepens (1946) wrote: everything helps, everything cures—from the moment the patient stops smoking. Lautenbach (1898b) forbade smoking but permitted chewing; Lillie (1934) permitted the smoking of cigarettes.

Of the drugs used in the treatment of tobacco amblyopia, the earliest and most popular appears to have been strychnine. Hypodermic injections of strychnine were thought to hasten recovery materially (Chisolm, 1878; Nelson, 1880; Webster, 1880; Armaignac, 1887; Ray, 1887; Black, 1891; Kerr, 1901); sometimes, potassium iodide was administered along with strychnine (Buxton, 1888; Lautenbach, 1898a, b; Finlay, 1901; Bär, 1906).

Hartridge (1886) treated 20 cases of tobacco amblyopia by total discontinuance of smoking; in one half of the cases, strychnine was administered, in the other half, a placebo with apparently equally good results. As late as 1923, Dinkelspiel used digitalis in conjunction with nux vomica in the treatment of this disease. Carroll (1935a) recommended abstinence for all his patients but the few who insisted on getting some medicine were given strychnine and a few received a single inhalation of amyl nitrite or an injection of sodium nitrite.

Vasodilating nitrites were first employed by Powers in 1886, who found inhalations of amyl nitrite of great value in cases of tobacco amblyopia. Other writers have reported the successful treatment of toxic amblyopia with other nitrites: sodium nitrite (Turtz, 1933; Cordes and Harrington, 1935); erythrol tetranitrate (Cordes and Harrington, 1935); nitroscleran (Pflimlin, 1930; Duggan, 1935). However, Carroll (1937) had no success from the use of sodium nitrite, which did not hasten the rate of recovery of his patients, and P. J. Evans (1939) also reported he had little or no success with vasodilators in the treatment of tobacco amblyopia.

According to Duggan (1937), visual improvement was more rapid in patients treated with acetylcholine, but it was greater in patients treated with sodium nitrite. Cragg (1936) and Orr (1936) also reported good results in patients treated by intramuscular injection of acetylcholine.

In a case reported by Galtier (1902), abstinence for 20 months failed to accomplish improvement in vision but treatment with pilocarpine was promptly followed by very definite improvement. Lillie (1934) recommended abstaining from cigars, pipes, or chewing tobacco and added that, usually, one course of pilocarpine sweats improved the vision to normal limits.

Loureiro (1865) recommended sedatives, particularly codeine, in the treatment of various forms of tobacco ophthalmias. Danis

(1912) treated four cases of tobacco amblyopia with intramuscular lecithin; two reacted favorably, two were not much benefited.

As Heaton, McCormick and Freeman (1958) pointed out, many workers have recognized the importance of the nutrition and general health of the patient with tobacco amblyopia and it has been suggested that a deficiency of one or more members of the vitamin-B group may be an etiologic factor and the response to vitamin-B complex and yeast has been studied.

Carroll (1935a) felt there were certainly important factors in the causation and progress of tobacco-alcohol amblyopia besides tobacco and alcohol. Because of his successful use of proper diet in the treatment of alcoholic polyneuritis despite continued consumption of alcohol (he allowed patients with tobacco-alcohol amblyopia to continue to smoke and drink as much as they had while contracting the disease) while maintaining them on a high-vitamin diet (supplemented by powdered brewer's yeast and yeast extract, wheat germ, cod-liver oil, and liver-extract injections) or on diets supplemented with brewer's yeast, vitamin-B complex or thiamine (Carroll, 1937, 1943, 1944, 1945). The speed of recovery in such patients appeared to be at least as good as in patients previously studied who had abstained from tobacco and alcohol.

Cushman (1939) relieved a patient with optic neuritis by the administration of large doses of vitamin B, and he emphasized the etiologic factor of vitamin-B deficiency in optic neuritis of alcohol or tobacco origin. Johnson (1939, 1941) reported several cases of toxic amblyopia in which there was complete recovery following adequate thiamine therapy, notwithstanding the continued use of tobacco and alcohol.

Gottlieb (1941, 1942) described a case of tobacco-alcohol amblyopia successfully treated by thiamine and vitamin-B complex, although the patient continued smoking. Maxwell (1953) presented two cases of tobacco-alcohol amblyopia which he relieved, partially in one case, completely in the other, by diminishing their tobacco and alcohol consumption slightly and instituting a proper diet including thiamine. He concluded that the thiamine deficiency was a more important factor than tobacco and alcohol excess. Hamilton (1957) reported that, under a regime of abstaining from tobacco and administration of vitamin-B complex, the paracentral scotoma in a subject with tobacco amblyopia disappeared in three months.

In contrast to the foregoing authors, however, Benedict (1949) stated that recovery of vision in tobacco amblyopia, unlike that in alcoholic amblyopia, could not be brought about by ingestion of vitamins alone but only after the use of tobacco had been discontinued.

Although large doses of vitamin-B complex are still considered to be indicated in tobacco-alcohol amblyopia (Carroll, 1956; Crain, 1958; Brit. M. J., 1:1582, 1959), it is the opinion of Heaton, et al. (1958) that such clinical trials as those mentioned have not convincingly shown that it is the deficiency of vitamin-B complex which is the cause of tobacco amblyopia. In many cases, they remark, smoking had been stopped; this alone improves most cases; and in addition, often the diet and drinking habits of the patients had been altered.

Heaton, McCormick and Freeman (1958) gave cyanocobalamin (vitamin B_{12}) to nine patients with tobacco amblyopia, of whom three continued smoking as heavily as before. All recovered more rapidly than would have been expected with the prohibition of smoking and with vitamin-B complex alone (six patients had initially had this orthodox treatment). Parenteral cyanocobalamin in dosage of 100 μg. was first given once or twice weekly for a month (once a day for the first 14 days to their anemic patients), then every fortnight for two months and finally at intervals of one month. They stated that probably it is safe to stop treatment after six months, provided that the visual fields are normal and there is no evidence of

Addisonian pernicious anemia or neurologic involvement. Their experience in this clinical trial suggested to them that much larger doses of cyanocobalamin would have been even more rapidly effective.

In summary, they state: "In this limited clinical trial the effect of parenteral cyanocobalamin in improving visual acuity and completely reversing the changes in the visual field has been most encouraging, even if the use of tobacco is continued."

Wokes (1958) has offered a theoretic explanation of the beneficial effects of vitamin B_{12} on tobacco amblyopia which was said to provide a basis for the practical treatment or prevention of this disease by administration of vitamin B_{12}, preferably oral, in frequent small doses, supplemented perhaps with thiamine and other B vitamins.

Following a selected review of the literature to this date, Rucker (1938) stated that current opinion favored the following therapeutic measures in tobacco amblyopia: (1) imperative abstinence from tobacco but not necessarily from alcohol in moderation if adequate diet is supplied; (2) eliminative measures (which, however, Rucker felt did not increase the elimination of tobacco toxins); (3) the administration of vasodilators (amyl nitrite, sodium nitrite, acetylcholine); (4) nourishing diet, since lowered nutritional states and vitamin deficiency are factors predisposing to poisoning by tobacco.

It seems safe to say that opinion as of the date of this essay would agree with Rucker's first and fourth points, perhaps not regarding total abstinence from tobacco as imperative, and perhaps emphasizing the addition of vitamin-B complex to the nourishing diet.

Reviews

Rather extensive reviews of the literature of tobacco amblyopia have been published in past years (for example, by Derby, 1871; Groenouw, 1892; Birch-Hirschfeld, 1901; among others). Recent review articles on the subject have tended to be brief (for example those by Veil, 1931; Saraux, 1954)—another sign, perhaps, of the senescence of the disease! Uhthoff (1911) gathered a bibliography of 403 references on tobacco and alcohol and the eye, but bringing such a bibliography up to date would probably run into the law of diminishing returns.

As we stated in our introductory remarks, we have examined approximately 1,000 published case reports of tobacco or tobacco-alcohol amblyopia. Some of these cases present unusual features of mild interest but (perhaps) of no longer real clinical or scientific significance.

What is apparent from a consideration of such a mass of case histories—and this is true not only of toxic amblyopia—is that the picture of the disease is (if we may continue to use the terms of art) more "impressionistic" than "photographic." For the picture lies as much in the eye of the beholder as in, to pursue the same metaphor, the amblyopia of the patient.

This is because, as Ramsay (1895) long ago pointed out, many of the older ophthalmic surgeons used to ascribe to tobacco poisoning a large number of obscure forms of disordered or suspended visual function in which the etiology of the disease should have been assigned to some entirely different cause. And we may well suspect the authenticity of many cases other than those three initially described as tobacco-alcohol amblyopia by Jayle, Bérard and Bonnal (1955), which, upon full investigation by these scrupulous physicians proved to be due to other causes.

To revert to the theme of our introduction: the true natural history of any disease is predicated first and foremost upon its proper diagnosis. To the same degree that this may be suspect, its natural history rests upon insecure foundations; the higher the structure erected thereupon, the more shaky the ultimate clinical and scientific conclusions.

Tobacco amblyopia was once, as we have seen, a towering structure indeed and its ruins are both impressive and monitory. But

within these ruins, as within those of many an ancient architectural monument, some of the inner chambers remain still intact. Thus, while the existence of tobacco amblyopia may not be denied, how many cases of it really exist in the vast literature of the subject?

And still another question arises: If the clinical picture and histopathologic findings are indistinguishable in "pure" tobacco amblyopia, in "pure" alcohol amblyopia, and in still other "forms" of retrobulbar neuritis in which the patient neither smokes nor drinks, how is it possible (without blunting Occam's razor) to postulate three separate and distinct "causes" for what is apparently the same condition? Is it not in better conformity to the dictates of logic to postulate *one* cause and *three* (or more) "precipitating" or "aggravating" or (at any rate) nonetiologic factors? And, finally, should not this same logical process be extended to all "tobaccogenic" diseases which are also found indistinguishably in nonusers of tobacco?

Medical College of Virginia (19).

ACKNOWLEDGMENT

We wish gratefully to acknowledge the kindness of Dr. L. Benjamin Sheppard, assistant clinical professor of ophthalmology, Medical College of Virginia, for his helpful and critical review of this manuscript.

BIBLIOGRAPHY

Adrogue, E.: La amblyopia alcohólica—nicotinica exabusu en el consultorio externo del hospital Santa Lucia. Semana med., **2**:320-322, 1923.

de Andrade, G.: Amblyopias toxicas—Alguns casos interessantes. Brazil-Méd., **2**:153-158, 1923.

Armaignac, H.: Amblyopie nicotinique rapidement guérie par la suppression du tabac et les injections hypodermiques de strychnine. Rev. clin. ocul., Paris, **8**:55, 1887.

Bachstez, E.: Bericht über die Häufung von Fällen retrobulbärer Neuritis und toxischer Amblyopie. Klin. Monatsbl. f. Augenh., **64**:393-398, 1920.

Bachstez, E., and Purtscher: Ueber die Haufung retrobulbärer Neuritiden einschliesslich toxischer Amblyopien gegenüber der Zeit vor dem Kriege. Ztschr. Augenh., **44**:38-44, 1920.

Bär, K.: Untersuchungen bei Tabak—Alkohol—Amblyopie. Arch. f. Augenh., **54**:391-399, 1906.

Benedict, W. L.: Etiology and treatment of optic neuritis. Texas State J. Med., **45**:126-130, 1949.

Bernheimer: Bemerkungen über die Tabaks—und Alkohol—Amblyopie und über reflectorischen Nystagmus, Klin. Monatsbl. f. Augenh., **39**:702, 1901.

Berry, G. A.: Note on tobacco amblyopia in women with remarks. Ophth. Rev., **3**:101-104, 1884.

———: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **7**:91-92, 1887.

Berry, G. W.: On central amblyopia. Royal London Ophth. Hosp. Rep., **10**:44-55, 1882.

Bettman, J. W., Fellows, V., and Chao, P.: The effect of cigarette smoking on the intraocular circulation. A.M.A. Arch. Ophth., **59**:481-488, 1958.

Bidault, R.: Amblyopie alcoolo-nicotinique et circulation rétinienne. Bull. soc. ophtal. Paris, 1936, p. 269-272.

Binet, L., and Crosnier, R.: Hypoalimentation et hyporésistance á l'alcool et au tabac. Progr. méd., Paris, **73**:275-277, 1945.

Birch-Hirschfeld, A.: Zur Pathogenese der chronischen Nicotinamblyopie. Arch. f. Ophth., **53**:79-112, 1901.

Black, G. M.: Strychnine nitrate in toxic amblyopia from alcohol and tobacco with a report of cases. N.Y. State J. Med., **54**:287-288, 1891.

Brognoli, C., and Citterio, M.: La Funzionalita Epatica Nell' ambliopia alcoolico-tabagica. Boll. ocul., **30**:12-38, 1951.

Browne, E. A.: Notes on tobacco-amblyopia. Liverpool Med.-Chir. J., **14**:107-126, 1888.

Bull, C. S.: Observations on toxic amblyopia, including course, prognosis, and treatment. N.Y. State J. Med., **22**:247-258, 1875.

Buxton, A. St. C.: Tobacco amblyopia. Lancet, Lond., **1**:367, 1888.

Carroll, F. D.: Analysis of fifty-five cases of tobacco-alcohol amblyopia. A.M.A. Arch. Ophth., **14**:421-434, 1935a.

———: Cerebrospinal-fluid studies in ten cases of tobacco-alcohol amblyopia. Am. J. Ophth., **18**:720-723, 1935b.

———: Importance of diet in the etiology and treatment of tobacco-alcohol amblyopia. A.M.A. Arch. Ophth., **18**:948-962, 1937.

———: "Alcohol" amblyopia, pellagra, polyneuritis, report of ten cases. A.M.A. Arch. Ophth., **16**:919-926, 1936.

———: The etiology and treatment of tobacco-alcohol amblyopia, Tr. Am. Ophth. Soc., **41**:385-431, 1943; Am. J. Ophth., **27**:847-863, 1944.

———: Recurrence of tobacco-alcohol amblyopia. Am. J. Ophth., **28**:636-638, 1945.

———: Toxic Amblyopia. Tr. Am. Acad. Ophth., **60**:74-82, 1956.

Carroll, F. D., and Franklin, C. R.: Tobacco amblyopia; alcohol amblyopia. Report of one uncomplicated case of each condition. Am. J. Ophth., **19**:1070-1072, 1936.

Carroll, F. D., and Ireland, P. E.: Association of toxic deafness with toxic amblyopia due to tobacco and alcohol. A.M.A. Arch. Otolaryng., **21**:459-463, 1935.

Chisolm, J. J.: Poisonous effects of tobacco on eye-sight. Virginia M. Month., **5**:749-751, 1878.

———: An interesting case of tobacco amblyopia in a lady. Am. J. Ophth., **4**:68-71, 1887.

———: Tobacco amblyopia. J.A.M.A., **14**:224, 1890.

Cohen, C. B.: Tobacco amblyopia. Brit. M. J., **2**:72, 1959.

Connor, L.: Tobacco amblyopia. J.A.M.A., **14**:217-225, 1890.

Cordes, F. C., and Harrington, D. O.: Toxic amblyopia due to tobacco and alcohol. Treatment with vasodilators; a report of eight cases. A.M.A. Arch. Ophth., **13**:435-444, 1935.

Cossu, A.: Ambliopia alcoolico-nicotinica. Note cliniche e statistiche, Boll. ocul., **2**:297-328, 1923.

Cragg, B. H.: The treatment of tobacco amblyopia by acetyl-choline. Bristol Med.-Chir. J., **53**:237-238, 1936.

Crain, Jr., P.: Optic and retrobulbar neuritis. J. Louisiana M. Soc., **110**:92-100, 1958.

Cushman, B.: The etiological factor of vitamin B deficiency in peripheral neuritis and optic neuritis of alcoholic or tobacco habitués. M. Woman's J., **46**:30, 1939.

Danis, M.: Traitement de l'amblyopie nicotinique par la lécithine. Progr. méd. Paris, **14**:11-12, 1912.

Derby, R. H.: Color-blindnes, and its acquisition through the abuse of alcohol and tobacco, N.Y. State J. Med., **13**:284-290, 1871.

Dinkelspiel, M. R.: Digitalis in the treatment of tobacco amblyopia: Preliminary contribution. N.Y. State J. Med., **117**:639-640, 1923.

Doggart, J. H.: Smoking as a factor in visual disturbance. Practitioner. London., **182**:204-211, 1959.

Dorrell, E. A.: Sensory pupil reflex in tobacco amblyopia, Lancet, Lond., **1**:1316, 1913.

Dowling, F.: The influence of tobacco on vision. Cincinnati Lancet-clin., **29**:585-590, 1892.

———: Tobacco and the eyes. Lancet-clin., **99**:699-702, 1908 (also listed as vol. 60).

———: The French government tobacco factory at Issy, near Paris. Hygienic Notes. J.A.M.A., **53**:1171-1173, 1909.

Doyne, R. W.: Observations on tobacco amblyopia. Royal Lond. Ophth. Hosp. Rep., **12**:51-58, 1889.

Doyne, P. G.: The scotomata of tobacco amblyopia. Brit. J. Ophth., **6**:1-9, 1922.

Duggan, W. F.: Vascular basis of tobacco amblyopia: Treatment with nitroscleran. A.M.A. Arch. Ophth., **13**:1059-1079, 1935.

———: Treatment of tobacco amblyopia with vasodilators. J.A.M.A., **109**:1354-1359, 1937.

Dunn, P.: Tobacco amblyopia. The Hospital, **48**:105-107, 1910.

Eales, H.: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **7**:54-61, 1887.

———: Tobacco amblyopia in women. Brit. M. J., **1**:963, 1890.

Edmunds and Nettleship: Central amblyopia in diabetes. Ophth. Rev., **2**:28-30, 1883.

Edwards, F., McKeown, T., and Whitfield, A. G. W.: Association between smoking and disease in men over sixty. Lancet, Lond., **1**:196-200, 1959.

Elderton, E. M.: An analysis of the consumption of tobacco and alcohol in cases of tobacco amblyopia: Part II. Detailed statistical discussion. Ann. Eugenics, **2**:266-289, 1927.

Ely, E. T.: Observations upon the effects of tobacco. N.Y. State J. Med., **31**:367-383, 1880.

Éperon: Sur quelques symptomes tabétiformes de l'amblyopie toxique. Rev. méd. Suisse, Geneva, **10**:546-554, 1890.

Evans, A. T. G.: Tobacco amblyopia. Brit. M. J., **2**:72, 1959.

Evans, P. J.: Tobacco amblyopia. Tr. Ophth. Soc. U. Kingdom, **59**:241-249, 1939.

Ewing, C. C.: Tobacco amblyopia. Brit. M. J., **2**:244-245, 1959.

Farnarier, F.: Scotome central fugace par angiospasme d'origine nicotinique. Rev. otoneur., Paris, **6**:647-648, 1928.

von Fellenberg, Th.: Ueber den Nachweis und die Bestimmung des Methylalkohols, sein Vorkommen in den verschiedenen Nahrungsmitteln und das Verhalten der methylalkoholhaltigen Nahrungsmittel im Organismus. Biochem. Ztschr., **85**:45-118, 1918.

Filehne, W.: Ueber den Entstehungort des Lichtstaubes, der Starrblindheit und der Nachbilder: Zugleich ein Betrag zur Lehre von der chronischen Tabaksvergiftung. Arch. f. Ophth., **31**:1-30, 1885.

Finlay, C. E.: Alcohol and tobacco amblyopia in Cuba. A.M.A. Arch. Ophth., **30**:241-257, 1901.

Fisher, J. H.: The influence of nicotin on ganglion cells: Its bearing on the pathology of tobacco-amblyopia. Ophth. Rev., **20**:151-159, 1901.

Foerster: Lichtsinn bei Krankheiten der Chorioidea und Retina. Klin. Monatsbl. f. Augenh., **9**:337-344, 1871.

Frost, A.: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **7**:78-80, 1887.

Galezowski: Des troubles visuels consécutifs a l'abus du tabac. Rec. Ophtal., **4**:677-683, 1883a.

Galezowski: Discussion de la communication de M. le Dr. Vallin sur quelques accidents causés par le tabac. Ann. hyg., **11**:47-51, 1884. Rev. hyg., **5**:908-912, 1883b.

Galtier: Amblyopie nicotinique. Ann. Ocul., **128**:371-373, 1902.

Gjessing, H.: Tr. Ophth. Soc. U. Kingdom, **59**:249, 1939.

Gottlieb, B.: Vitamine "B" complex deficiency as a cause of retrobulbar neuritis and peripheral neuritis in a chronic alcoholic and pipe smoker. Brit. J. Ophth., **25**:556-564, 1941.

———: Vitamins in ophthalmology, Lancet, Lond., **1**:547, 1942.

Greeves, R. A.: Ophthalmology. Practitioner, London, **137**:593, 1936.

Griffith, A. H.: Tobacco amblyopia in women. Brit. M. J., **2**:1212, 1886.

———: Toxic amblyopia: Analysis of cases from the cliniques of Drs. Little and Glascott. Tr. Ophth. Soc. U. Kingdom, **7**:81-90, 1887.

Groenouw: Ueber die Intoxicationsamblyopie. Arch. f. Ophth., **38**:1-70, 1892.

———: Beiträge zur Kenntniss der concentrischen Gesichtsfeldverengerung. Arch. f. Ophth., **40**:172-223, 1894.

Guélliot, C.: Maladies Des Yeux. Amaurose nicotinique. Progr. méd., Paris, **5**:426-427, 1877.

Gunn, J. A.: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **50**:390-393, 1930.

Gunn, M.: Toxic Amblyopia, Tr. Ophth. Soc. U. Kingdom, **7**:67-71, 1887.

Gutierrez-Muro, F.: Tabaquismo. Clín. laborat., Zaragoza, **25**:217-230, 1934.

Gy, A.: La vision et l'audition dans l'intoxication tabagique chronique. Rev. internat. hyg. therap. ocul., **7**:49-53, 1913.

Hambresin, L., and Schepens, C. L.: L'Amblyopie tabagique. Ann. ocul., **179**:191-217, 1946.

———: Amblyopie tabagique et Atrophie optique hérédo-familiale, Ophthalmologica, **118**:751-763, 1949.

Hamilton, W. H. C. M.: Tobacco amblyopia. J. R. Nav. M. Serv., **43**:161-162, 1957.

Hanke: Bericht über die Häufung von Fällen retrobulbärer Neuritis und toxischer Amblyopie. Klin. Monatsbl. f. Augenh., **64**:393-398, 1920.

Harman, N. B.: The visual fields in tobacco amblyopia, Lancet, Lond., **2**:821-822, 1904.

Hart, E.: Smoking as a cause of optic atrophy, etc. Lancet, Lond., **2**:141, 1863a.

———: Is amaurosis produced by tobacco? Lancet, Lond., **2**:201, 1863b.

Hartridge, G.: Tobacco amblyopia. Brit. M. J., **1**:200, 1886.

Heaton, J. M., McCormick, A. J. A., and Freeman, A. G.: Tobacco amblyopia: A clinical manifestation of vitamin-B_{12} Deficiency. Lancet, Lond., **2**:286-290, 1958.

———: Tobacco amblyopia. Brit. M. J., **2**:188, 1959.

Hedges, H. S.: Eye damage by tobacco. Virginia M. Month., **82**:544-545, 1955.

———: Tobacco amblyopia. Med. Times, **85**:1151-1152, 1957.

Herbolsheimer, A. J.: Color and color perception. J. Aviation M., **13**:201-215, 1942.

Hine, M. L.: Tobacco amblyopia in a woman. Lancet Lond., **1**:597-598, 1920.

Hirschberg, T.: Tobacco and alcohol amblyopia. Brit. M. J., **2**:810-811, 1879.

Hirschler, I.: Ueber den Missbrauch von Spirituosen und Taback als Ursache von Amblyopie. Arch. f. Ophth., **17**:221-236, 1871.

Horner: Über die Intoxicationamblyopie. Corr.-Blatt Schweiger Aerzte, **8**:396-399, 1878.

Hutchinson, J.: Clinical data respecting amaurosis, more especially respecting that form of it supposed to be induced by tobacco. Lancet, Lond., **2**:536-538, 1863.

———: Statistical details of four years experience in respect to the form of amaurosis supposed to be due to tobacco. Ophth. Hosp. Rep., **7**:169-185, 1873.

———: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **7**:61-67, 1887.

Jayle, G. E., Bérard, J., and Bonnal, J.: Les fausses névrites optiques alcoolo-tabagiques. Bull. soc. ophtal. France, **8**:569-572, 1955.

Jendralski, F.: Die Intoxikationsamblyopie (Tabak, Alkohol) vor, in und nach dem Kriege. Deutsche med. Wchnschr., **48**:1207-1209, 1922.

Johnson, L. V.: Alcohol-tobacco (toxic) amblyopia treated with thiamin chloride. A.M.A. Arch. Ophth., **21**:602-603, 1939.

———: Clinical ocular conditions associated with vitamin-B-complex deficiencies. Am. J. Ophth., **24**: 1233-1240, 1941.

Kerr, J.: Tobacco amblyopia in daily practice: With analysis of fifty consecutive cases seen in 1900. Quart. M. J. Yorkshire, p. 231-240 (May) 1901.

Keyser: Tobacco amblyopia, J.A.M.A., **14**:225, 1890.

Kretschmer, W.: Die "elektive Giftwirkung" bei gewissen Formen der Inhalations-vergiftungen in anatomisch-funktioneller Betrachtungsweise. Schweiz. med. Wchnschr., **72**:421-422, 1942.

Krimsky, E.: Symmetric incomplete annular scotoma of tobacco origin without enlargement of the blind spot. Am. J. Ophth., **17**:722-725, 1934.

Krimsky, E.: Defective vision due to tobacco and alcohol. Sight-Saving Rev., Summer, 1936a; Abstract in New England J. M., **215**:86, 1936b.

Kruger, A.: Ueber ophthalmoskopisch nachweisbare Gefässveränderungen bei zentralem Skotom infolge Tabak-Alkohol-Amblyopie und Arteriosklerosis cerebri. Klin. Monatsbl. f. Augenh., **49**:579-608, 1911.

Lautenbach, L. J.: Med. News, **49**:552-553, 1886.

———: Some results in cases of tobacco amblyopia. J.A.M.A., **31**:770-771, 1898a.

———: Some results in cases of tobacco amblyopia. Ophth. Rec., **7**:419-420, 1898b.

Lawford, J. B.: Stationary tobacco-amblyopia in a man subsequently affected by diabetes. Ophth. Rev., **2**:28, 1883.

———: Optic nerve atrophy in smokers. Brit. M. J., **1**:1072, 1890.

Leber, Th.: Ueber das Vorkommen von Anomalien des Farbensinnes bei Krankheiten des Auges, nebst Bemerkungen über einige Formen von Amblyopie. Arch. f. Ophth., **15**:26-107, 1869.

Leishman, R.: Gastric function in tobacco amblyopia. Tr. Ophth. Soc. U. Kingdom, **71**:319-327, 1951.

Lewis, F. P.: Preliminary note on that form of toxic amblyopia produced by tobacco. J. Ophth. Otol. & Laryng., **13**:399-402, 1901.

Lillie, W. I.: The clinical significance of retrobulbar and optic neuritis. Am. J. Ophth., **17**:110-119, 1934.

Lindner: Bericht über die Häufung von Fallen retrobulbärer Neuritis und toxischer Amblyopie. Klin. Monatsbl. f. Augenh., **64**:393-398, 1920.

Lokshima, S. Y.: Tobacco toxicoses (in Russian). Sovet. Vestnik Oftal., **8**:464-468, 1936.

Lopez, E.: Ambliopia nicotinica. An. Oftal., **2**:205-206, 1900.

Loureiro, J. C.: Influence du tabac a fumer sur les maladies des yeux., Communication made to the Ophthalmologic Congress at Heidelberg in 1865 and which has since been put into a special brochure. Abstracted in Klin. Monatsbl. f. Augenh., **3**:394-396, 1865.

Lyle, D. J.: Changes in the visual fields confirmed by pathological diagnosis. J.A.M.A., **133**:517-521, 1947.

Lyle, H. W.: The effect of tobacco in health and disease. (f)—on the eyes. Practitioner, London, **75**: 68-71, 1905.

Maxwell, H. W.: Tobacco-alcohol (toxic) amblyopia. Texas State J. Med., **49**:137-140, 1953.

Meany, W. B.: Tobacco amblyopia. Med. Rec., **73**:532, 1908.

Meyerhof, M.: Beobachtungen über Tabakschädigungen der Sehnerven im Orient und in Deutschland. Klin. Monatsbl. f. Augenh., **66**:107-111, 1921.

Moore, W. O.: Diabetic affections of the eye. N. Y. State J. Med., **47**:339-347, 1888.

Morton, A. S.: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **7**:71-73, 1887.

Nelson, J.: On tobacco-amblyopia. Brit. M. J., **2**:774-775, 1880.

Nettleship, E.: Notes on the diagnosis of tobacco amblyopia. St. Thomas' Hosp. Rep., N. S., **19**:51-74, 1879.

———: Toxic Amblyopia. Tr. Ophth. Soc. U. Kingdom, **7**:36-53, 1887.

Nettleship, E., and Edmunds, W.: On central amblyopia in diabetes, especially as to its dependence on, or independence of, tobacco smoking. Tr. Ophth. Soc. U. Kingdom, **3**:165-178, 1882-83.

Neuschueler, I.: Ambliopie nicotiniche. Lettura Oftal., **6**:399-429, 1928.

Noyes: Tobacco amblyopia. J.A.M.A., **14**:224-225, 1890.

Nuel, J. P.: Altérations de la macula lutea. Arch. Ophtal., **16**:473-484, 1896.

Nuel, J. P. (Translated by F. W. Marlow): The toxic amblyopias. Ann. Ophth., **11**:169-200, 1902.

Orr, H. C.: Acetylcholine in tobacco amblyopia. Brit. M. J., **2**:69-70, 1936.

Orzalesi, F.: La pressione arteriosa retinica nell 'ambliopia alcoolico-nicotinica. Bol. Ocul., **17**:889-897, 1938.

Parsons, J. H.: Action of nicotin upon nerve cells. J. Physiol. London, **26**:38-39 (Proceedings), 1901a.

———: Note on the pathology of toxic amblyopias. Brit. M. J., **1**:1400, 1901b.

———: Further note on the pathology of toxic amblyopias. Ophth. Rev., **20**:181-189, 1901c.

Percival, A. S.: Some things I do not know. Brit. M. J., **2**:513, 1925.

Peter, L.: Discussion of paper by deSchweinitz and Fewall on diabetics and tobacco amblyopia. Am. J. Ophth., **9**:618-619, 1926.

Pflimlin, R.: Die Behandlung der Alkohol—Tabaksamblyopie mit Nitroskleran. Klin. Monatsbl. f. Augenh., **85**:787-795, 1930.

Pick, L.: Ueber einige Kriegsfolgen bei Augenleiden. Deutsche Med. Wchuschr., **46**:44-45, 1920.

Poulard: Amblyopie toxique par l'alcool et le tabac. Progr. méd., Paris, **24**:115-117, 1908.

Powers, G. H.: Diagnosis and treatment of tobacco amblyopia. Med. News, **49**:642, 1886.

Ramsay, A. M.: Tobacco amblyopia. Lancet, Lond., **1**:1174-1177, 1895.

Ray, J. M.: Three cases of tobacco amblyopia, showing the results gained by hypodermic injections of strychnia. Southwest. Med. Gaz., **1**:262-265, 1887.

Riddell, W. J. B.: The early stages of tobacco amblyopia. Glasgow M. J., **125**:268-274, 1936.

Rivet, L.: La toxicité du tabac et de ses ersatz. Press méd., **56**: 258-259, 1948.

Rodiet, A., and Cans, F.: Diagnostic différentiel des troubles cerébraux d'origine toxique dus a l'alcool et au tabac et de la paralysie générale d'apres les symptomes oculaires. Ann. Med.-Psychol., 9s, **4**:408-420, 1906.

Ruata, V.: Considérations sur le nicotinisme, l'amblyopie nicotinique et leur traitement. Clin. Ophtal., **14**:3-11, 1925.

Rucker, C. W.: Treatment of tobacco-alcohol amblyopia. Am. J. M. Sc., **195**:274-277, 1938.

Sachs, T.: Anatomisch-klinischer Beitrag zur Kenntniss des Centralscotoms bei Sehnervenleiden. Arch. f. Augenh., **18**:21-50, 1888.

Salva, M.: Le champ visuel périphérique dans l'amblyopie toxique. Ann. Ocul., **117**:254-259, 1897.

Samelsohn, J.: Zur Anatomie und Nosologie der retrobulbären Neuritis (Amblyopia centralis). Arch. f. Ophth., **28**:1-110, 1882.

Saraux, H.: Incidences ophtalmologiques de l'intoxication tabagique. France méd., **17**:23-26, 1954.

Sattler, C. H.: Ueber die Ursachen der Tabak-Alkohol-Amblyopien nach dem Kriege. Klin. Monatsbl. f. Augenh., **70**:318-325, 1923.

Schieck, F.: Ueber Zusammenhang gewisser Formen der retrobulbären Neuritis mit Erkrankungen des Gefässystems. Arch. f. Ophth., **56**:116-131, 1903.

Scholtz, K.: Statistisches über Tabak-Alkohol-Amblyopie. Klin. Monatsbl. f. Augenh., **45**:187-197, 1907.

Schrumf-Pierron, P.: Tobacco and Physical efficiency: A Digest of Clinical Material. New York, Hoeber, 1927.

deSchweinitz, G. E.: Toxic amblyopia with cases. (Society Proceedings.) Am. J. Ophth., **5**:386-388, 1922.

———: Tobacco amblyopia, Lancet, Lond., **2**:604, 1927.

deSchweinitz, G. E., and Edsall, D. L.: Concerning a possible etiological factor in tobacco-alcohol amblyopia revealed by an analysis of the urine of cases of this character. Am. J. M. Sc., **126**:216-227, 1903a; Reviewed in Lancet, Lond., **2**:771-772, 1903b.

deSchweinitz, G. E. and Fewell, A. G.: Diabetes and tobacco amblyopia. Therap. Gaz., **50**:623-628, 1926.

Shannon, C. E. G. and McAndrews, L. F.: Diabetic and tobacco amblyopia: Report of a case. A. M. A. Arch. Ophth., **11**:757-762, 1934.

Shears, C.: Tobacco amblyopia. Brit. M. J., **1**:1199-1202, 1884.

Sichel: Amaurosis following tobacco-smoking. Union méd. May 5, 1863a.; Abstract in Brit. For. Chir. Rev., p. 265, 1863b.; Am. J. M. Sc., **46**:549-550, 1863c.; Abstract in Ann. Therap., **24**:103-112, 1864.

———: De l'influence du tabac fumer sur la production de l'amaurose. Union Méd., **17**:236-240, 1865a.

———: Nouvelles recherches pratiques sur l'amblyopie et l'amaurose causées par l'abus due tabak a fumer, avec des remarques sur l'amblyopie et l'amaurose des buveurs. Ann. Ocul., **53**:122-136, 1865b.

Smith, F. P. E.: Tobacco amblyopia. Brit. M. J., **2**:123, 1959.

Snell, S.: On the relations of some occupations to the eyesight. Ophth. Rec., **4**:161-177, 1894a.; Brit. M. J., **2**:584-585, 1894b.

Spicer, H.: Cas de névrite optique rétrobulbaire. Ann. Ocul., **115**:58, 1896.

Stewart, D. D. S.: Tobacco amblyopia. Brit. M. J., **2**:98, 1959.

Terrien, F.: Des troubles visuels dus a l'abus de l'alcool et due tabac. Ann. Hyg. Pub., 4th series, **9**:97-133, 1908.

Thompson, A. H.: Tobacco amblyopia: Some cases in which the interval between cessation of smoking and improvement of vision was unusually long. Royal Lond. Ophth. Hosp. Rep., **14**:406-410, 1897.

Traquair, H. M.: Incidence of tobacco amblyopia in Edinburgh and district, Lancet, London, **2**:603-604, 1927. Also published in more detail under, "Tobacco amblyopia" Lancet, Lond., **2**:1173-1177, 1928.

Traquair, H. M.: Toxic amblyopia. Tr. Ophth. Soc. U. Kingdom, **50**:372-385, 1931.

Treitel, Th.: Ueber den Werth der Gesichtsfeldmessung mit Pigmenten für die Auffassung der Krankheiten des nervösen Sehapparates. Arch. f. Ophth., **25**:29-130, 1879.

Turtz, C. A.: Toxic amblyopia—Treatment with vasodilators. J. Am. Inst. Homeop., **26**:511, 1933.

Uhthoff, W.: Beitrag zur Sehnervenatrophie. Arch. f. Ophth., **26**:244-282, 1880.

———: Untersuchungen über den Einfluss des chronischen Alkoholismus auf das menschliche Sehorgan. Arch. f. Ophth., **32**:95-188, 1886; **33**:257-318, 1887.

———: Beziehungen d. Allgemeinleiden zu Veranderungen d. Sehorganes. 2. Nikotinvergiftung. Graefe-Saemisch Handb. ges. Augenh., **11**:25-45, 1911.

Usher, C. H.: An analysis of the consumption of tobacco and alcohol in cases of tobacco amblyopia. Ann. Eugenics, **2**:245-261, 1927.

Vandegrift, G. W.: Tobacco amblyopia. Med. Rec., **85**:980-982, 1914.

van der Hoeve: Tobacco amblyopia. Lancet, Lond., **2**:604, 1927.

van Millingen: Toxic amblyopia. Ophth. Rev., **7**:63, 1888.

Veil, P.: L'amblyopie toxique alcoolonicotinique. J. Praticiens, **45**:375-376, 1931.

de Vincentiis, G.: Qualche considerazione sull'importanza del fattore tossico "nicotina" nella genesi della cosidetta "amblyopia alcoolico-nicotinica." Rev. oto-neuro-oftal., **4**:281-284, 1927.

Voigt, W.: Der gegenwartige Stand der Lehre von der Tabak- und Alkoholamblyopie mit Benutzung des Materials der Giessener. Universitäts-Augenklinik. Inaug.-Dissert., Giessen, 1906, 29 pages.

Volokonenko, A. I.: The influence of the tobacco on the eyes of the workers in the tobacco industry. (In Russian.) Oftal. Zhurnal, **4**:288-289, 1925.

Webster, D.: Amblyopia from the abuse of tobacco and alcohol. Med. Rec., **18**:649-655, 1880.

Weekers, R.: L'intoxication chronique par le tabac. Rev. méd. Liège, **4**:573-576, 1949.

Wokes, F.: Tobacco amblyopia. Lancet, Lond., **2**:526-527, 1958.

Wordsworth, J. C.: Report of three cases of amaurosis produced by tobacco. Lancet, Lond., **2**:95-96, 1863a.

———: Is amaurosis produced by tobacco? Lancet, Lond., **2**:172-173, 1863b.

Wray, C.: Tobacco amblyopia. Lancet, Lond., **1**:429-430, 1905.

THE WHITE LIMBUS GIRDLE OF VOGT*

H. Saul Sugar, M.D., and Sidney Kobernick, M.D.
Detroit, Michigan

The white limbus girdle was described by Vogt,[1] in 1921, and Koeppe,[2] in 1922, as a symmetrical white opacity lying in the interpalpebral zone of the cornea either at the limbus or separated from the limbus by a very small clear interval.

Vogt described two types of white limbus girdle:

Type I was represented by a white band, chalky in appearance, with holes at several points (fig. 1). It was separated from the sclera by a clear interval and had no prolongations on the central side.

Type II was shown as a white band, also chalky, with either a relatively clear interval or no clear interval between the limbus and the girdle (fig. 2). It differed from Type I especially in that there were no holes and in that there were prolongations on the central edge of the opacities, suggesting that they were related to the terminal portions of the pallisades and limbal capillaries.

In order to study the white limbus girdle a clinical and histopathologic investigation was undertaken. Clinically, the course and incidence of the condition were studied, together with its relation to age and sex. For the histologic study, 13 small biopsies were obtained during cataract operations. Further histologic studies were made on six eye-bank eyes from patients over 57 years of age. Each of the eyes was prepared so that representative limbal areas were obtained from horizontal, vertical and upper diagonal meridians.

During the entire period of this study and the examination of the limbal areas of 200 patients, only one example of the Type I white limbus girdle was found. Since then two other examples have been observed. De-

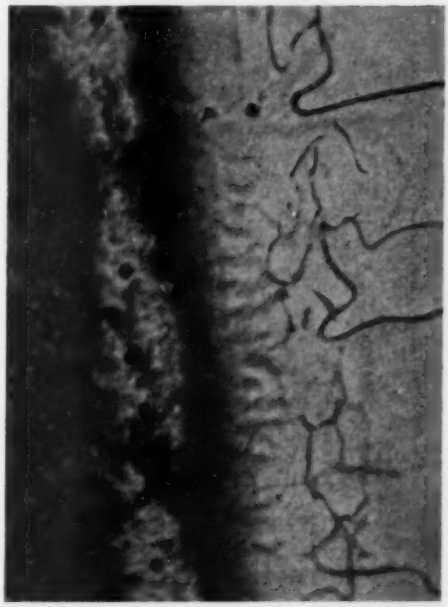


Fig. 1 (Sugar and Kobernick). Type I white limbus girdle of Vogt showing white band with roundish holes and clear interval. (From Vogt, A.: *Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges.* Berlin, J. Springer, 1930.)

Toledo,[3] in his study of this subject, stated that he had never encountered such a case. This study is essentially that of Type II white limbus girdle. Its relation to the Type I lesion will be discussed.

Location and Incidence

The white limbus girdle (Type II) is always located in the interpalpebral area of the cornea and its length depends entirely on the size of that area (figs. 3 and 4). In prominent eyes it was found that the interpalpebral area increases toward the lower limbus and in such eyes the girdle may be found along the entire lower limbus. It is interesting that in such cases, if a pinguecula is present, it involves the same zone.

* From the Departments of Ophthalmology and Pathology, Sinai Hospital of Detroit and Wayne State University College of Medicine.

Fig. 2 (Sugar and Kobernick). Type II white limbus girdle of Vogt, showing typical picture with little or no true clear interval and prolongation on central side. (From Vogt, A.: *Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges.* Berlin, J. Springer, 1930.)

The white limbus girdle was not always present in equal degree in the four limbal areas in the interpalpebral fissure zone. It was 1.7 times more frequent on the nasal side than on the temporal side; yet occasionally it was more prominent temporally than nasally. At times it was found to be present in one of the four corneal margins and not in the other three areas (table 1).

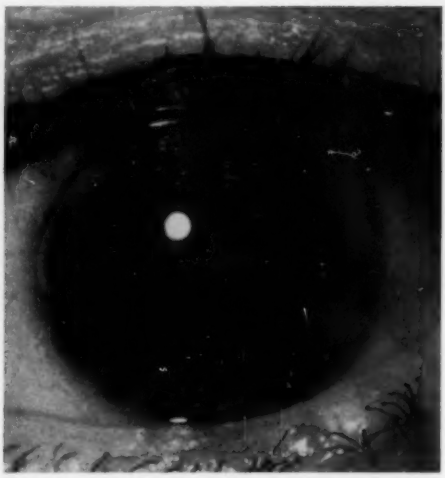


Fig. 3 (Sugar and Kobernick). Clinical photograph of white limbus girdle. Type II.

The limbus girdle has been considered as a rare condition (Duke-Elder[4]). Our study of its incidence indicated that it was present in 60 percent of all patients over 40 years of age. However, when observed directly with the slitlamp beam it was recognizable in only 15.5 percent of patients over the age of 40 years, but when indirect lateral illumination was used, the condition was visible in 44.5 percent more. The method of illumination shows up the girdle by a combination of scleral scatter and retroillumination.

Age incidence

A white limbus girdle was rarely found in persons under the age of 40 years. A few were seen in patients in the 30s. In a series of 200 consecutive normal patients 40 years of age or over such a girdle was noted in four positions in the interpalpebral areas at the corneal margins of both eyes. The findings are noted in Table 1. In the 40-49 and 50-59 year groups, a girdle was found in 54.9 percent, either by direct illumination biomicroscopy or by retroillumination. In the older age groups the incidence increased to 66.6 percent in the 60-69 year group, 92.8

percent in the 70-79 year group and 100 percent in the 80-89 year group.

The increasing incidence of white limbus girdle visible by direct illumination indicated that the girdles increased in density with age. In the 40 to 49 year group 21.8 percent of the limbus girdles were visible by direct illumination. In the 50-59 year group the incidence of directly visible girdles was 20 percent, in the 60-69 year group 69.2 percent, in the 70-79 year group 44.4 percent and the 80-89 year group 100 percent.

The white limbus girdle was found to be present in about equal frequency in males and females, as indicated in Table 2.

Histologic findings

The histologic picture of the white limbus girdle is basically similar to that of the pinguecula and pterygium. It consists of the same remarkable hyperplasia of elastic tissue fibers with fragmentation (figs. 5, 6 and 7). Collagenous hyalinization is slight. No significant inflammatory component was present in most. Vascular pallisades could be seen in the limbal zone of the normal areas and could not be considered as part of the lesion, nor should they be mistaken for pannus, as has been pointed out by Zimmerman.[5]

Our findings differ somewhat from those of deToledo,[3] who described the histopathology of the white limbus girdle as subepithelial hyaline degeneration with hypotrophy of the epithelium. He found a deposition of calcium in Bowman's membrane more toward the cornea. In some places the calcification extended into the epithelium. Perpendicular sections showed areas which suggested capillaries surrounded by calcium. Our findings differ (1) in that the white limbus girdle does not involve an area where Bowman's membrane is present, (2) our histologic studies showed both hyaline degeneration, though slight, and the marked hyperelastosis already described.

Only one of the biopsy specimens showed what is usually recognized as calcium deposition in Bowman's membrane. This was not near the area of hyaline change and suggests that the calcium deposits occur only in places where Bowman's membrane is present, more corneal than the area of the white limbus girdle.

Fig. 4 (Sugar and Kobernick). The clear interval shown here is only relative.

Special staining with PTAH, PAS and Sudan IV was done. Phosphotungstic acid-hematoxylin stains indicated that the material was not fibrin. Periodic acid-Schiff stains showed no unusual polysaccharide characteristics. Sudan IV stains of frozen sections proved that the lesions were devoid

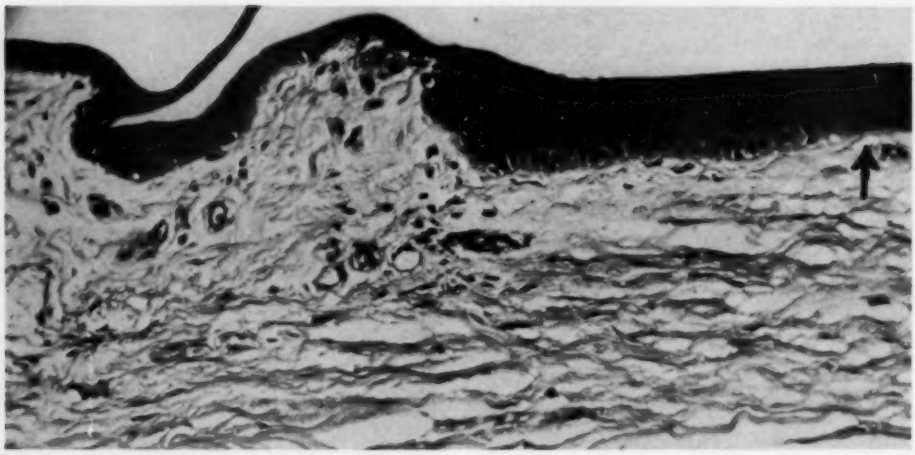


Fig. 5 (Sugar and Kobernick). Section from normal limbus of enucleated eye, showing the structure of the normal limbus. The end of Bowman's membrane is indicated by the arrow at the extreme right. The remainder of the section constitutes the limbus. Note the vascularization in the left half of the photograph, also the paucity of elastic tissue fibers as well as their fine, wavy appearance and parallel arrangement. (Weigert elastic-haematin, phloxine, saffron ×280.)

of stainable fat, although the neighboring arcus senilis of the cornea could be shown to contain fat.

Discussion

After making these observations, it became apparent that many of the problems relating to the white limbus girdle, such as its relation to Vogt's Type I lesion and the findings in Bowman's membrane by de-Toledo, are directly related to the definition of the term limbus.

Salzmann[8] considered the limbus to be "a zone of about one mm. width limited centrally by the margin of Bowman's membrane and peripherally by the corneoscleral border

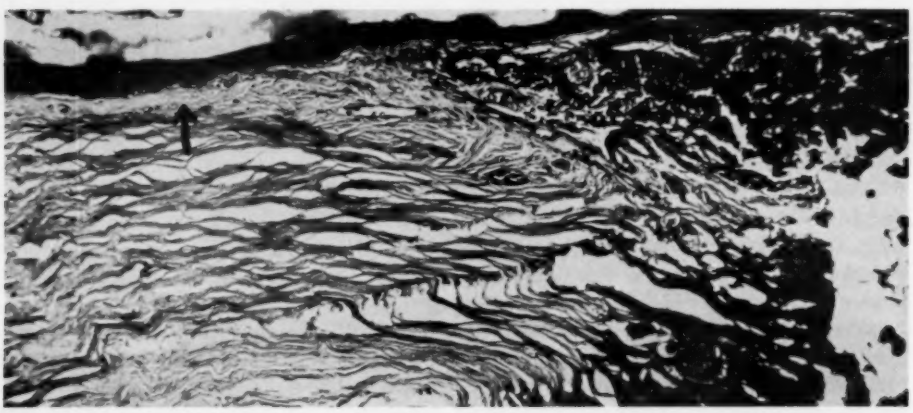


Fig. 6 (Sugar and Kobernick). Section from a white limbus girdle lesion in the limbus of the same eye as Figure 1. This shows the end of Bowman's membrane on the left (arrow). The vascular limbus is occupied by hyperplastic, tortuous and fragmented elastic tissue fibers. The blackening at the lower right is artefact. (Weigert—HPS, ×135.)

TABLE 1

INCIDENCE OF WHITE LIMBUS GIRDLE

Age Group (yr.)	No. Patients	Appearance of Corneal Margins in Interpalpebral Areas*					Percentage of Eyes with White Limbus Girdle	
		Temporal Area O.D.	Nasal Area O.D.	Nasal Area O.S.	Temporal Area O.S.	Summary of All Areas		
40–49	71	X—3 I—18 O—50	X—4 I—32 O—35	X—7 I—30 O—34	X—2 I—18 O—51	X—7 I—32 O—32	54.9	
50–59	80	X—1 I—23 O—56	X—7 I—37 O—36	X—6 I—37 O—37	X—2 I—21 O—57	X—7 I—37 O—36	54.9	
60–69	30	X—6 I—9 O—18	X—9 I—11 O—13	X—12 I—13 O—8	X—4 I—12 O—17	X—9 I—13 O—11	66.6	
70–79	14	X—2 I—7 O—5	X—4 I—9 O—1	X—4 I—9 O—1	X—1 I—8 O—5	X—4 I—9 O—1	92.8	
80–89	2	X—1 I—1 O—0	X—2 I—0 O—0	X—2 I—0 O—0	X—1 I—1 O—0	X—2 I—0 O—0	100.0	
TOTAL	200	X—13 I—58 O—129	X—26 I—89 O—85	X—31 I—89 O—80	X—10 I—60 O—130	X—31 I—89 O—80	15.5 44.5	60.0

* X = white limbus girdle by direct illumination.
I = visible by indirect illumination.
O = no limbus girdle.

and, properly speaking, includes only the anterior layers of the cornea."

Since the white limbus girdle always lies outside the end of Bowman's membrane, it is, therefore, strictly speaking, in the limbus and not in the cornea proper.

It is also obvious from our observations that the limbus width varies not only from patient to patient but in the various areas of the same eye, so we might better define the limbus topographically as a variable translucent area between the end of Bowman's membrane and the line of scleral opacity. It is more properly related to the conjunctiva in its superficial layers and to the cornea in its deeper part.

Usually the upper limbus is the widest and the nasal and temporal limbuses are narrowest. The varying width above is especially important in performing a trephining operation. Where the limbus is especially wide, there is no problem with a thin epithelial bleb since the limbal area dissects easily from the stroma and no dissection into Bowman's membrane is necessary. On the other hand, a narrow limbus above increases

TABLE 2

SEX INCIDENCE OF WHITE LIMBUS GIRDLE

Age Group (yr.)	Sex	No. Patients	Incidence of White Limbus Girdle	Percentage of Incidence
40–49	F	49	26	53.0
	M	22	13	59.0
50–59	F	53	28	52.8
	M	27	16	59.2
60–69	F	20	14	80.0
	M	13	8	61.5
70–79	F	7	7	100.0
	M	7	6	85.7
80–89	F	2	2	100.0
TOTAL	F	131	77	58.7
	M	69	43	62.3

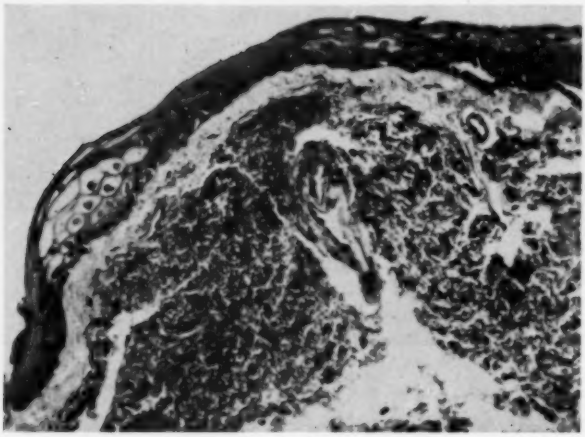


Fig. 7 (Sugar and Kobernick). Section from a surgically excised white limbus girdle, showing the detailed structure composed of an hyperplasia and fragmentation of the elastic fibers. Note the hyaline connective tissue which is continuous with the normal collagen of the cornea and sclera separating the elastic from the epithelial tissue. (Weigert-HPS X370.)

the danger of a thin bleb and of buttonholing. In fact, the width of the limbus above may be used in determining whether or not this operation is best suited for the individual patient.

These findings suggest a change in describing the location of surgical incisions. At present we usually state that an incision is so many mm. behind the limbus when we mean behind the corneolimbal junction. However, the limboscleral junction is a fixed location, even though not always very sharp, while the corneolimbal junction is more variable in its location, not only because of anatomic variations but because pannus formation tends to move the corneolimbal junction more toward the cornea by its frequent tendency to destroy Bowman's membrane. Therefore, we might better use the limboscleral junction as the point of reference for descriptive purposes.

Let us relate our present descriptions of the limbus to the lesions described by Vogt. In patients with band-shaped opacity of the cornea in whom a white limbus girdle was present, it was possible to determine with the slitlamp that a clear interval was present between the two and that the white limbus girdle was not as superficial as the band opacity. These findings and the infrequent observation of the Type I girdle of Vogt suggest that the involvement of Bowman's membrane is a purely coincidental finding and is more related to band opacity than to the limbus girdle.

In fact, three observations point to the idea that the white limbus girdle (Type II) is a component of a conjunctivolimbal interpalpebral triad composed of the pinguecula, its sequel, the pterygium, and the white limbus girdle. These observations are:

1. Each of these lesions is located within the interpalpebral area. Since the interpalpebral area is not always the same in all eyes it is obvious that when a pinguecula is present in an unusual area, the white limbus girdle, if present, involves exactly the same area.

In eyes which are prominent, if a pinguecula is present in the lower portion of the eye and involves the lower limbus, the white limbus girdle involves the corresponding area. It should be pointed out that, although both may be present in the same area, each may be present grossly without the other. In prominent eyes with pingueculae on the lower portion of the globes, if a pterygium forms, it occurs in the same position. The relation between pterygium and pinguecula has been pointed out.[6]

2. Each member of the triad shows histologically material which takes elastic tissue

stains. Cogan[7] suggests this probably is pseudoelastic tissue. Hyaline degeneration is present in all eyes though it is slight in the limbus girdle.

3. All of the conjunctivolimbal triad are more frequently found in the nasal interpalpebral area. In a paper on the pinguecula Sugar and Kobernick[6] pointed out that the greater incidence in the nasal area is probably caused by firmer pressure of the lids nasally due to the greater curvature of the orbicularis on the nasal side. It is suggested that the same explanation holds for the white limbus girdle.

These observations suggest that, notwithstanding the relative immobility of the limbal area, there is still some mechanical squeezing effect of the lids on the interpalpebral area of the limbus and that this common trauma is somewhat related to the hyperelastosis and degenerative changes present in all of the limbal triad. One must, of course, consider other possible factors, such as inflammation, common physical agents, and even heredity.

Conclusions

Observations on the white limbus girdle of Vogt (Type II) suggest that this condition is a subepithelial hyperelastosis with degeneration almost identical to the pinguecula and the pterygium, the three conditions constituting an interpalpebral conjunctivolimbal triad. The Type I girdle is probably of an entirely different nature, more closely related to the band-shaped opacity of the cornea. Even in Vogt's picture there is a truly clear interval of clear cornea between the lesion and the limbus. It should, therefore, not be considered a white limbus girdle. Even though deToledo[3] found no cases of Type I clinically, his photograph of calcification of Bowman's membrane indicates that he actually was dealing with such a case.

The incidence of white limbus girdle is much greater than hitherto reported, occurring in 60 percent of all patients over 40 years of age, although it is visible by direct slitlamp illumination in only 15.5 percent.

The incidence of white limbus girdle increases with age, being approximately 55 percent in patients aged 40-60 years and significantly greater with each succeeding decade.

The limbus has been defined and the practical significance of variations in its width discussed.

18140 San Juan (21).

Acknowledgment

We gratefully acknowledge the technical assistance of Mr. Joseph Taylor of Sinai Hospital laboratories.

References

1. Vogt, A.: Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges. Berlin, Springer, 1930, v. 1, p. 114.
2. Koeppe, L.: Mikroskopie des Lebenden Auges. Berlin, 1922.
3. deToledo, C.: Sôbre o cinturão branco límbico de Vogt (Tipo II), Rev. Brasil. Oftal., **17**:53, 1958.
4. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, Mosby, 1938, p. 2004.
5. Zimmerman, L.: Personal communication.
6. Sugar, S., and Kobernick, S.: The pinguecula. Am. J. Ophth., **47**:34; 1959.
7. Cogan, D. G., Kuwabara, T., and Howard, J.: The nonelastic nature of Pingueculas. A.M.A. Arch. Ophth., **61**:388, 1959.
8. Salzmann, M.: The Anatomy and Histology of the Human Eyeball. (E. V. L. Brown, translator.) Chicago, Franz Deuticke, 1912, p. 28.

THE COLLECTION, STORAGE AND SELECTION OF HUMAN VITREOUS*

FOR USE IN RETINAL DETACHMENT SURGERY

G. KEITH EDWARDS, M.D., AND JOHN C. LOCKE, M.D.
Montreal, Quebec

Vitreous implantation in retinal detachment surgery is a comparatively recent development. The first successful series of implants was begun in 1949. With the appearance of the reports of Shafer and others, interest in the technique has steadily increased as encouraging results have been reported.[1-4]

In this paper our present technique for the collection, storage, and selection of vitreous is outlined. It is particularly applicable for general hospitals. The importance of a meticulous, standardized technique in all phases of handling this material cannot be stressed too much.

The danger of causing intraocular infection is constantly present. Early in our experience two cases of endophthalmitis occurred which were traceable to faulty technique. As a result of 12 months' experience with the following improved technique, we are confident that intraocular infection need not occur. We consider any less meticulous routine to be inadequate.

The importance of avoiding chemical contamination of the implant is also apparent when one considers the retinal damage that has been shown to occur following intravitreal injection of even small quantities of relatively nontoxic substances.[7]

Although the property of self-sterilization has been attributed to vitreous[3, 6, 8] refrigerated at 4°C., there are exceptions. Even a negative 48-hour blood agar culture is not to be relied upon completely; more extensive precautions are indicated to assure the sterility of the sample.

A. SOURCE OF VITREOUS

Our vitreous is obtained from post-mortem material at the Institute of Pathology, McGill University and is collected within a period of 24 hours after death. Only cases with an all-inclusive autopsy consent or a head and neck consent are utilized, to obviate any medicolegal problems.

The patient's case notes are available at the time of collection and the following are excluded as donors: (1) Those with a history of intraocular disease; (2) diabetics; (3) high myopes; (4) those with jaundice (obstructive or hemolytic); (5) children below the age of 16 years.

It has not been possible to make antemortem examinations of the donor eyes, although this would be most desirable.

B. WITHDRAWAL OF VITREOUS

The collection, storage, and culturing of vitreous should be the responsibility of a single individual, as experience is desirable and a relatively minor deviation from the routine could result in an unsatisfactory sample. The operating surgeon must have complete confidence in the purity of the sample.

A "vitreous tray" in a sterile pack is available at all times in the operating room. Contents of vitreous tray are: (a) sterile drapes; (b) eye drape; (c) lid speculum; (d) two pairs of toothed forceps; (e) two muscle hooks; (f) two No. 16 vials with No. 88 rubber apron stoppers;† (g) two 5.0 cc. syringes; (h) four 18-gauge needles. In addition there is, in a separate container, a bottle of 1/1,000 aqueous Zephiran, two pairs of sterile rubber gloves, and a mask.

* From the Department of Ophthalmology of the Royal Victoria Hospital and of McGill University. Presented before the Montreal Ophthalmological Society, November, 1958, and at the Montreal Sectional Meeting of the American College of Surgeons, April, 1959.

† Allergist's Supply Co., 458 Broadway, New York City. Screw top bottles are best avoided because of greater danger of contamination.

Technique of collection is as follows: The skin of the lids is prepared with 1/1,000 aqueous Zephiran. Gloves are changed, the eye is draped and the lid speculum inserted. Postmortem conjunctival adhesions are broken and the globe is adducted. A small site on the temporal conjunctiva, 8.5 mm. from the limbus is cauterized with a heated muscle hook. The 18-gauge needle is then introduced into the globe with the tip of the needle directed in a posteromedial direction, the target being the center of the vitreous body. Efforts are made not to disturb the retina and choroid opposite the point of entry. The vitreous is then aspirated slowly. The aspiration is limited to 1.5 to 2.0 cc. per globe.

As the globe collapses, care is taken to prevent contact of the needle tip with the retina and choroid. When the desired volume is obtained, the syringe is detached from the needle and the vitreous injected into a vitreous vial through a preplaced 18-gauge needle through the rubber stopper. An identical procedure is carried out on the other eye and this vitreous is injected into the same vial, giving a total volume of three to four cc. The globe is restored to its original contour by the injection of normal saline. The procedure causes no noticeable disfigurement to the eyes of the deceased.

Originally we used a 21-gauge needle for vitreous aspiration. This has been discarded in favor of the 18-gauge needle for the following reasons: (1) Easier aspiration with larger bore needle; (2) less disruption of the physical properties of the vitreous; (3) reduction in incidence of pigment and other debris in the aspirate.

C. Storage of vitreous

Following removal of vitreous, the vial is labelled with the donor's name and the date. A record is kept of the cause of death and age of the donor and the name of the recipient is recorded later.

The vials are placed in a refrigerator in a separate container for uncultured vitreous and kept at a temperature of 4°C. The temperature is periodically checked.

A second container in the refrigerator contains samples that have been cultured and found to be sterile. These are ready for use.

D. Culture of vitreous

The danger of creating a serious intraocular infection by introducing a contaminated implant into the eye must be constantly kept in mind. There are numerous references in the literature to the self-sterilizing properties of refrigerated viterous.[6,8] In general our experience coincides with these findings but there were exceptions. Early in our experience two vitreous samples accidentally contaminated with Streptococcus viridans and Aerobacter aerogenes, respectively, continued to give positive cultures despite prolonged refrigeration.

In some centers, reliance is placed on a blood agar culture and 48-hour incubation. Our experience has taught us the necessity of an enriched fluid medium (such as Brewer's) and the desirability of a five-day incubation. In two samples the culture was negative after 48 hours and positive for diphtheroids at five days.

Our present culturing technique is as follows: The vial is removed from refrigeration after seven days. A sterile table is prepared upon which are placed sterile tuberculin syringes and 23-gauge needles. The operator is masked, scrubbed, and gloved. The assistant prepares the tops of the vitreous vials with two-percent tincture of iodine followed by 70-percent alcohol, which are then allowed to dry. This is necessary to prevent entry of iodine or alcohol into the vial. Two minims of vitreous are aspirated through a 23-gauge needle and then injected into a tube of Brewer's medium through a sterile rubber top. The culture tube is incubated for five days during which time it is periodically checked for signs of growth. If there is no turbidity after five days, the vitreous sample is considered sterile and suitable for implantation.

E. Selection of sample for implantation

Each sample is selected on the basis of (a) sterility, (b) clarity and (c) color.

a. *Sterility* is determined by a negative five-day Brewer's-medium culture.

b. *Clarity.* A few samples, despite the standard collection procedure, are diffusely cloudy or show particles of pigment. These are discarded. The incidence of this complication has been reduced by use of the 18-gauge needle. The majority of samples, despite general clarity show nonpigmented floccular sediment. These are not discarded but, when aspirating at the time of surgery, an attempt is made to avoid them.

c. *Color.* All icteric samples are discarded. In our experience, grossly jaundiced patients have icteric vitreous and the more gross the jaundice, the deeper the yellow color of the sample.

Two hours before surgery, a sample containing at least 3.0 cc. is taken to the operating room and allowed to assume room temperature.

F. Summary

1. A technique for the collection, storage, and selection of human vitreous for use in retinal detachment surgery has been outlined.

2. The importance of a standardized approach to all phases of handling the material is emphasized. The more uniform the technique, the less chance of bacterial or chemical contamination of the sample.

The Royal Victoria Hospital (2).

References

1. Shafer, D. M.: The treatment of retinal detachment by vitreous implant. Tr. Am. Acad. Ophth., **61**:194-200, 1957.

2. Pischel, D. K.: (Discussion of paper by Shafer.) The treatment of retinal detachment by vitreous implant. Tr. Am. Acad. Ophth., **61**:194-200, 1957.

3. Shafer, D. M.: Chapter on Surgery of the vitreous. In Complications in Eye Surgery (Fasanella, R. M., Editor), Philadelphia and London, Saunders, 1957, pp. 256-262.

4. Moffat, P. McG.: Intravitreal vitreous in retinal detachment surgery. Tr. Ophth. Soc. U. Kingdom, **77**:61-87, 1957.

5. Shapland, C. D.: Intravitreal vitreous in retinal detachment surgery. Tr. Ophth. Soc. U. Kingdom, **77**:69-87, 1957.

6. Shafer, D. M., and Bussey, J. L.: Further experience with vitreous implants in old retinal detachments. A.M.A. Arch. Ophth., **60**:255-257, 1958.

7. von Sallmann, L.: Controversial points in penicillin therapy of ocular diseases. A.M.A. Arch. Ophth., **39**:752-804, 1948.

8. Reed, H. W., Tushingham, J. C., and Tushingham, G.: A preliminary report on the self-sterilizing property of vitreous. A.M.A. Arch. Ophth., **60**:361-365, 1958.

BEHIND THE IRON CURTAIN

Noel T. Simmonds, M.D.
Alexandria, Louisiana

From June 25 to July 17, 1959, was spent behind the iron curtain visiting eye clinics at Prague and Bratislava, Czechoslovakia; Krakow and Warsaw, Poland, and Stalingrad and Kiev, Russia. A hospital in Sochi on the Black Sea was also visited.

Our guides in Czechoslovakia and Poland were reluctant to express themselves on politics and those in Russia were all for Russia. Our guide in Bratislava was a communist and all for their system. Politics and conditions in general were not discussed with the ophthalmologists I had the pleasure of meeting but I met other people both in Czechoslovakia and Poland who talked freely, after looking around to see whether anyone was listening, especially in Czechoslovakia. There was much more freedom of expression in Poland.

In Czechoslovakia I was told that for each

4,000 people, there was a group of doctors consisting of a dentist, pediatrician, general practitioner, surgeon, obstetrician, and gynecologist with nurses, and so forth. Other specialists were in the larger towns and patients were referred to them from the neighborhood or small town polyclinic. A similar system seems to prevail in Poland and Russia. Patients hospitalized were assigned to a private room or to a ward by the doctor. The doctor and dentist worked eight hours per day but could work two hours more without assistance and with no extra pay. They saw fewer patients than in the old days as they worked less time. The Minister of Health in Czechoslovakia is a Roman Catholic priest who wears the garb of a priest and collaborates with the communists but is not recognized by the Vatican. An interesting sidelight is that in Czechoslovakia we saw many fields of white opium poppies.

Education is compulsory from the age of six to 14 years, then work in a factory or more school until the age of 17 years, and then to the university if the I.Q. is sufficiently high. The I.Q. was determined by a board of teachers, doctors, and so forth, who classified students as mentally fit for factory work or university students. There was no recourse. Children of workers used to be admitted without question while the children of former capitalists were denied university education without two years work in a factory to prove that they were good socialists. Apparently they found that the children of the workers as a group did not have sufficient mentality to measure up to the standards expected of university students so now all children must work in a factory one year and then all are admitted to the university regardless of their background if their I.Q. is sufficiently high. A similar pattern seems to operate in Poland and Russia. However, in Russia there are no ex-capitalist parents.

In Russia, doctors and university students have 10 years of grade school, 10 months per year. Doctors then went to medical institute for six years, which corresponds to our medical school, and one year of general internship. He or she then was ready for general practice at 850 rubles per month; lower than the average laborer's pay.

In Prague the Second Eye Clinic of the Medical Faculty of Charles University was visited. Prof. Dr. Jaromir Kurz was very gracious and courteous and made me welcome. He had unfortunately recently fractured an arm in a fall and was unable to operate himself. The surgery was done by his assistant (a woman physician) who was a very skillful operator. Incidentally, the majority of ophthalmologists in the iron curtain countries are women. Many operations were performed in this clinic in a large operating room with two tables running at the same time.

The tendon-lengthening, partial tenotomy was preferred to recession. This was done under local anesthesia on five- and eight-year-old children. In cataracts, a preplaced black silk suture which they called a Roggenkampfer suture is used. This consists in taking a bite in the cornea about two mm. from the limbus and parallel to it at the 12-o'clock position with a double-armed suture and then going under the tendon of the superior rectus with both and tying it over the superior rectus tendon. A Graefe knife incision and one peripheral iridectomy are done at the 12-o'clock position. Intracapsular extraction is preferred. They had used some alpha chymotrypsin from Spain. Prof. Kurz does many corneal grafts. The university operates a laboratory for research on corneal physiology.

Here I also met an ophthalmologist from Carlsbad, Dr. Blahoslav Rejchrt, who was director of the hospital there. He was very enthusiastic over the "New Siberian" treatment of chemical burns of the conjunctiva to prevent symblepharon. He recently wrote me, giving me details of the treatment which are as follows:

The necrotic conjunctiva should not be removed when cleaning the eye of the corrosive material. Injections of the patient's blood with penicillin are

applied daily under the burnt conjunctiva in the following manner: if the entire conjunctival surface is affected, about 4.0 ml. of solution is necessary. Two ml. of blood is added to 2.0 ml. of physiologic saline containing 50,000 units of penicillin. Novocain is given before or added. We try to inject the blood-penicillin mixture through a single puncture under the entire upper and lower bulbar conjunctiva which bulges out. The same procedure is continued daily though in lesser amounts. Part of the blood escapes through the previous sites of puncture.

After several days the eyelids cease to stick to each other and the conjunctiva remains smooth and shining. We administer the injections for 10-14 days, more commonly less. Not epithelized cornea is covered with ointment, the intrabulbar pressure is checked.

Prof. Rejchrt also enclosed a copy of a paper he had presented which had a well-documented bibliography. He also stated that "good results with this method of treatment has now been confirmed in a number of countries (Prof. Colen, USSR, Dr. Karpowicz, Poland, Prof. Campos, Italy, Universitatsaugenklinik, Halle, Germany, several clinics in Czechoslovakia, the method now being included in textbooks of ophthalmology in Poland and CSR.)"

At Bratislava the eye clinic of the Medical Faculty of the Slovak University was visited. Prof. Dr. Anton Gala was, like Prof. Kurz, very courteous and cordial. They were not operating the day I was there so we had more time to talk and exchange information. The Graefe incision was preferred, using a preplaced double-armed corneoscleral mattress suture and two peripheral iridectomies in cataract extractions. In glaucoma, a Graefe type basal iridectomy was done for acute congestive glaucoma and an iridencleisis for glaucoma simplex. Peripheral iridectomies were not done and tonography was not done. The obliques were rarely operated except in cases of muscle paralysis.

Prof. Gala kindly showed me an excellent colored movie of an operation he had developed for retinal detachments, being a form of scleral imbrication. An equatorial incision was made and the sclera split anteriorly instead of posteriorly as most of us prefer in this country. No polyethylene tubes, and so forth were used.

In Krakow, Poland, I visited the clinic of Dr. Marian Wilczek, who was away on holiday. His clinic, however, was very ably conducted by his gracious and charming assistant and very skilful surgeon, Dr. Jania Sokolowska. Among other operations, she performed a myectomy of the inferior oblique, inserting a large round needle in the lower cul-de-sac at the junction of the outer and middle thirds to the bony floor of the orbit and along the floor and out in the semilunar fold, picking up the inferior oblique and exposing it very well. A tendon-lengthening tenotomy, using a tongue of the middle half of the tendon, was preferred to a recession. Dr. Sokolowska also took us to lunch to an eye hospital in the outskirts for scrofula, strabismus, and trachoma, scrofula being their term for phlyctenulosis and not tuberculosis. A high-vitamin fresh-vegetable as well as meat diet was served us, being one of the best meals we had on this trip. Diet, vitamins, steroids, and antihistamines were used in scrofula, and aureomycin, terramycin, and sulfonamides in trachoma, reducing the hospital stay to about three months instead of the two or three years, as formerly. Orthoptics and pleoptics (Cüppers) were given the children with strabismus and an operating room was being completed at the time of my visit.

In Warsaw I met Prof. Wladyslaw Melanowski, a very gracious gentleman of the old school who unfortunately is soon retiring because of age. He will be very hard to replace. He showed me three of his textbooks on ophthalmologic subjects which were very interesting and which I am sure would have been well accepted in our country if it were not for the language barrier. He is currently working on a history of ophthalmology in pictures which he showed me and which will be most interesting.

In Russia one cannot simply go to an eye clinic and be welcomed as in the West and in Poland and Czechoslovakia. The medical attaché at the U. S. Embassy in

Moscow, Dr. McClendon, told me that no one would be admitted in this manner. Unless you are a member of a delegation, the visit must be handled through Intourist, the government monopoly travel agency. After repeated requests, the Intourist man at the Hotel Ukrainia made a phone call and told me that it was "impossible" to visit the Institute of Helmholtz and on my persistent request called again and said it was closed on Monday. I was also told that it was closed on Saturday afternoon and Sunday, which I question.

Intourist telegraphed ahead to Stalingrad and arranged for me to visit the hospital there with an interpreter. The head of the Department of Ophthalmology was Mrs. Effete. She was very cordial and gracious and it was distinct pleasure to talk to her, even through an interpreter. Her cataract technique was retrobulbar injection and pressure on the globe, dilate with adrenalin, Graefe incision with conjunctival bridge, complete iridectomy in old patients but no iridectomy in young patients, intracapsular extraction, no sutures; she claimed no prolapsed irises. Both eyes are closed and the patient is kept in bed three days. She had not used alpha chymotrypsin but said it was being used in Czechoslovakia.

In acute glaucoma, miotics and carbonic anhydrase inhibitors were used for 24 hours and then a Graefe-type basal iridectomy with ab externo incision was done. In glaucoma simplex, miotics were used as long as possible, then an iridencleisis was performed. They did gonioscopies but no tonography.

In retinal detachments, retinopexy is preferred. Scleral resection was done in large tears, and so forth. The patients were kept in bed three weeks then used pinhole goggles and were back at work in three months. No polyethylene tube implants were used. In strabismus, a tendon-lengthening tenotomy was preferred to a recession.

Mrs. Effete also showed me a knife sharpener based on electrolysis of the blade in a solution of orthophosphoric acid and chromic anhydrite for one minute. I tested a knife sharpened in this manner on a drum and found it satisfactory.

In Sochi, a resort on the Black Sea, a hospital using warm hydrogen sulfide water for many things, including baldness, was visited. An interpreter said that the doctor prescribed the exact temperature, concentration, duration and frequency of treatment and that the water was "too strong to take treatments every day," all of which probably assisted in getting the best results possible by suggestive treatment. The water was also inhaled in the nostrils and chest as a mist, used as a douche, as a mouthwash for pyorrhea, and baths for arthritis, and so forth.

In Kiev, the third city in Russia, the eye clinic of the Kiev Medical Institute under Prof. Panel Savovich Pletas was visited. The first thing he showed me with a laugh was an "Arkansas Oil Stone" made by Pike Manufacturing Company of Pike, New Hampshire, which he used to sharpen cataract knives, examining them with a slitlamp before using them. He told me that the electrolysis sharpening method previously mentioned was all right if there were no irregularities on the blade but that, if there were irregularities, they had to be worked out on the stone.

His cataract technique was retrobulbar injection of Novocaine, Van Lint akinesia if he had a nervous patient, adrenalin and cocaine drops, Graefe incision and simultaneous capsulotomy with the Graefe knife, wide conjunctival bridge and extracapsular cataract extraction. No iridectomies were done, no sutures were placed and, as in Stalingrad, he claimed no prolapsed irises. Eserine and pilocarpine were used the first postoperative day and then the pupil was dilated. The patients were up on the third day. In acute glaucoma, a Graefe basal iridectomy is done. In glaucoma simplex, the Elliott trephining operation or cyclodialysis is preferred. Iridencleisis was not done due to fear of complications. In congenital glaucoma, cyclo-

dialysis was preferred. In retinal detachments, retinopexy was preferred but an occasional scleral resection was done. No polyethylene tube or implant was used. In squints, recession and resection was preferred. The obliques were operated on only in cases of muscle paralysis.

Prof. Pletas told me that he had a collection of many cases of cysticercus in his laboratory which he was going to show to me but after we had talked for about two hours it was time to go and the collection was forgotten, which I regret. He also showed me an interesting foreign-body extractor similar to those developed by Rolf.

As in Moscow, it was impossible for me to get into the hospital in Leningrad in spite of all my efforts, including the subterfuge of having a private guide-interpreter take me to a neighborhood polyclinic to have my own eyes examined. The ophthalmologist was a woman who took my history, vision, examined the fundi, and tensions with a small applanation type tonometer without finding anything wrong. She then told me I would be referred to another clinic for a more detailed examination with my pupils dilated in a day or two. I was leaving for Finland the next day so was unable to pursue it any further. I then identified myself as an ophthalmologist and invited her to have lunch with the interpreter and me. She, however, declined as she had to go home during her lunch hour to look after her child.

The tonometer was about three cm. long and dumb-bell shaped, the ends being covered with a flat glass or plastic surface which was applied dry to the cornea and then applied to a paper that was discolored by the wet spot on the end of the tonometer in contact with the cornea. The diameter of this wet spot was measured and, the softer the eye, the larger the spot. The color of the spot on the paper looked like fluorescein.

I failed to write it down but was told at one of the clinics visited that, in acute congestive glaucoma, instead of doing a broad basal iridectomy, three small peripheral iridectomies through the same keratome incision were sometimes done. I do not remember where this was.

Incidentally, in Czechoslovakia the professors have a private practice. This is also true in Poland where it is all right for anybody to have a private practice but nobody but the professors earn enough to be able to rent an office or to buy instruments to equip it. We were also told that some of the outstanding doctors in Russia had private practices.

In Russia many of the spectacle frames were made of brown plastic, usually with the nose piece being a simple band resting on the bridge of the nose and the temples coming off from the center, similar to frames used in this country a good many years ago. The frames worn by a large percentage of persons wearing glasses who were passed on the streets were poorly adjusted, one lens being several mm. higher than the other. Comparatively few people on the streets of Russia wore glasses, however, and those who did wear them looked as if they were wearing rather strong corrections.

Comment

Our colleagues behind the iron curtain were very courteous and cordial and as interested in exchanging knowledge as I was. My conclusion was that our technique in cataract extraction, in certain features, notably sutures, is better; that we seem to be ahead of them in more widespread use of tonography, in the use of Chandler's peripheral iridectomy instead of a complete basal iridectomy in selected cases of narrow-angle glaucoma and, possibly, in more widespread treatment of congenital glaucoma by goniotomy or goniopuncture. We also seem to be ahead of them in surgery of the obliques and in the more frequent use of scleral resection, imbrication, buckling, and so forth, in unfavorable cases of retinal detachment. They are ahead of us in obtaining tissues for grafting, and so forth since cadavers of patients dying in a hospital belong to the state.

The Russians have a translation service

which translates foreign journals and which, I was told, mails to all doctors a list of translations available every month.

The Russian educational system is rigid. Students go to school to study without the diversion of extracurricular activities. They do not celebrate a football victory or drown their sorrows over a defeat every Saturday night. They are moving fast and will prove themselves to be competitors of the first rank.

It should be borne in mind that these observations and conclusions are based on short visits to a small number of clinics and interviews carried on through a nonmedical interpreter not very familiar with medical terminology, so some allowances must be made for unintentional mistakes in translation.

It is my sincere hope that, if and when our ophthalmological colleagues behind the iron curtain are able to come to the United States, ophthalmologists whom they visit will be as cordial and courteous to them as they were to me.

1300 Jackson Street.

STUDIES ON THE EFFECT OF CORALOX, A CHOLINERGIC ORGANIC PHOSPHATE, ON THE EYE*

MAURICE KADIN, M.D.
Chicago, Illinois

The toxicology and pharmacology of a number of cholinergic organic phosphates have been the subject of many investigations in recent years.[1] The present investigation was initiated to study the pharmacologic effects of one of these compounds when instilled in the eye.

The compounds selected for screening included coralox, dipterex, vinyl dipterex and Lilly 21315. Solutions in oil or water were instilled into the eyes of rabbits and observations made as to the extent and duration of miosis. It was found that coralox, the oxygen analogue of Co-Ral, exhibited the strongest and most prolonged miotic activity of this group in the rabbit eye. Co-Ral (diethyl-0-3-chlor-4-methyl-7-coumarinyl phosphorothionate) is used for the control of ectoparasites. The active metabolite of Co-Ral is the oxygen analogue and is produced in the liver by replacement of the sulfur by an oxygen atom. The sulfur analogue has little if any miotic activity.

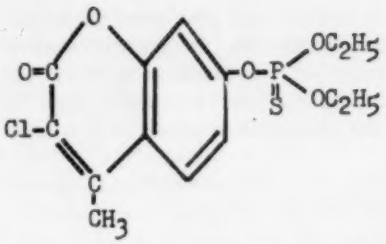
Coralox has no commercial use and is only slightly water soluble. It is stable to a maximum of one-percent solution in peanut oil for at least six months. The pharmacology of coralox has been investigated by DuBois, Schmalgemeier and Plzak (to be published).[2] Their investigation showed that the toxicity was within the range of that exhibited by DFP, TEPP and Mintacol. It is a potent anticholinesterase agent, and penetrates the blood-brain barrier.

Until 1957, the only organic phosphate compounds utilized in the eye therapeutically were DFP (diisopropyl fluorophosphate), Mintacol (p-dinitrophenyl diethylphosphate) and TEPP (tetraethyl pyrophosphate). The use of the latter compound was discontinued because of chemical irritation. These compounds are all potent anticholinesterase agents. The search for a longer acting, more potent agent for the lowering of intraocular pressure in glaucoma has recently led to the study of new organic phosphates and quaternary ammonium cholinergic compounds.

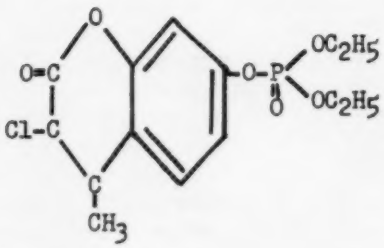
The chemical nerve impulse transmission theory presented by Loewi (1921)[3] is the basis for understanding the cholinergic activity of anticholinesterase drugs which protect acetylcholine against hydrolysis by cholinesterase. Other pharmacologic actions may

---

* From the Department of Surgery (Ophthalmology), The University of Chicago.



Co-Ral



Oxygen analogue of Co-Ral

Fig. 1 (Kadin). Chemical structure of Co-Ral.

be included in the individual characteristics of the compound.

The principal groups are divided into (a) reversible and (b) irreversible anticholinesterases:

The first group includes physostigmine and choline esters, which are related structurally to acetylcholine, are general esterase inhibitors, and produce a complex with cholinesterase which is readily broken.

The compounds which irreversibly bind cholinesterase include the polyalkylphosphates, which are characterized by long duration of action, and are structurally different from acetylcholine. The irreversibility is relative, and is based on the rate with which it is possible to dissociate the enzyme-inhibitor complex. The effects of the strongest irreversible drugs such as echothiophate or Phospholine Iodide are reversed by use of oximes such as 2-PAM (Pyridine-2-aldoxime methiodide) (Mamo and Leopold, 1959),[4] while DFP requires both 2-PAM and atropine to counter peripheral and central effects respectively.

Oximes are considered to act in part at least by regeneration of drug-inhibited cholinesterase (Kewitz and Nachmansohn, 1957).[5] The actions of anticholinesterase compounds such as coralox, TEPP, Mintacol, and so forth, are also blocked by atropine and homatropine, which are effective by blocking the response of cells to accumulated acetylcholine.

Polyalkylphosphates have been known since 1932. The studies of Adrian, Kilby and Kilby (1940),[6] and Adrian, Feldberg, Kilby and Kilby (1941)[6] showed that their great toxic effect was based on their anticholinesterase activity. These compounds were studied in Germany, Great Britain and the United States secretly during the Second World War, and many of these studies are not available. DFP was synthesized in 1932 by Lange and Krueger[7] in Germany and was reinvestigated by McCombie and Saunders[8] in 1941, and by Adrian, Kilby and Kilby (1942),[6] who found that it had greater inhibiting activity than methyl esters previously known. In 1944, Schrader[9] developed Mintacol (p-dinitrophenyl diethylphosphate) and reported his studies in 1950. It has had extensive use in Europe as a miotic in glaucoma. DuBois and Mangun (1947)[10] reported the anticholinesterase activity of tetraethyl pyrophosphate (TEPP), and hexaethyl pyrophosphate (HETP) and the anticholinesterase activity of Mintacol in 1949.

Phospholine Iodide (217 MI) or echothiophate and its tertiary analogue (217 AO) were studied in 1952 by Burgen and Chipman and in 1956 by Koelle and Steiner[11] and by Schaumann and Job,[12] who found that Phospholine Iodide was the more desirable compound of these two because it did not pass the blood-brain barrier and thus has lower systemic toxicity. They demon-

strated that it did not lower brain cholinesterase levels more than slightly. This compound is a potent anticholinesterase drug which is water soluble. It is stable at 5°C. indefinitely, but under ordinary room conditions, for three weeks. It acts on the eye in low concentrations of 0.1 and 0.25 percent. One drop has an action that produces miosis and tension lowering that lasts for periods of up to three weeks (Leopold and Gold).[13] Toxic symptoms due to ciliary spasm include browache and headache, which are controlled by salicylates; occasional diarrhea and abdominal pain. It has the ability to lower red blood cell specific cholinesterase. As with miotics in general, in children iris cysts are often demonstrated. Fibrinous exudation into the anterior chamber is also found in chronic simple glaucoma with use of phospholine, and may lead to dense posterior synechias (Becker, Pyle and Drews).[14]

BC-48 (demecarium bromide, or Humorsol) or decamethylene bis-N-methyl-carbaminoyl m-3 methyl ammonium phenol was studied in 1957 by Gitler and Pillat[15] and also in 1959 by Miller, Divert and Crouzet[16] as well as others. It is water soluble, stable for one month, and its action on the eye lasts three days or more, with marked miosis, spasm and lowering of tension, accompanied by conjunctival hyperemia and pain. In one percent solution it can overcome mydriasis and cycloplegia produced by one percent atropine. It is not an organic phosphate, but is an extremely potent anticholinesterase agent requiring special care on ocular instillation, and a special caution warning on the package.

New Russian anticholinesterase agents include tetra-ethylmonothiopyrophosphate (A2), which appears to have the same characteristics as TEPP, of which it is an analogue. It is not water soluble or stable, but proved to be effective as a miotic in the treatment of glaucoma (Ustimenko).[17]

Anticholinesterase agents have only a slight effect on the eye when given systemically even in toxic doses and miosis is notable in animals only in lethal doses (Koelle and Gilman, 1949).[18] Under normal conditions absorption of chemicals instilled in the eye occurs through the conjunctiva as well as the nasal mucous membrane by drainage via the lacrimal canals. No systemic symptoms following ocular instillation of polyalkylphosphates were observed by Grant (1948)[19] and several German investigators. Toxic symptoms such as nausea, diarrhea, sweating, salivation, fall in blood pressure, were reported by Sugar (1951)[20] with physostigmine.

Leopold and Comroe[21] reported that DFP changed the serum values for cholinesterase of man, dog and cat. Abraham (1953)[22] reported nervous symptoms—tic, bedwetting, nausea, and staggering—in children on DFP. Salivation and muscle tremors were noted by Leopold and Comroe with ocular instillation in animals (cats, dogs) of two drops of DFP one percent, and by Marr and Grob (1950)[23] with one drop of four percent TEPP. Five percent neostigmine has frequently caused toxic symptoms and vomiting (Rosengren, 1943).[24] DFP, phospholine and BC-48 probably present the strongest of these drugs with prolonged miosis, ciliary spasm, headache and changes in intraocular pressure. With DFP, miotic activity and tension lowering ability in normal eyes that is greater than in glaucomatous eyes were mentioned by Leopold and Comroe[21] and Wheeler.[25]

Maximal miosis can be produced by all these drugs, but the duration and time of onset vary. Miosis occurs in five to 20 minutes and lasts up to three weeks, varying with the compounds. Miosis does not parallel the effect on accommodation, which has a shorter duration, and also varies with compounds and species of animal.

Toxicity of these organic phosphate compounds depends on various factors, such as solubility, absorption, hydrolysis and rate of cholinesterase resynthesis. Toxic symptoms are due to the accumulated acetylcholine, with earliest symptoms being similar to the effects of muscarine, which include sweating, lacrimation, salivation and muscle fibrilla-

tion. Physostigmine, neostigmine and choline esters have protective action against polyalkylphosphates, and atropine prevents muscarinelike symptoms, but does not abolish the nicotinelike spasms, which are antagonized by magnesium ion (Goodman and Gilman),[6] Scholz,[26] Leopold and Comroe,[21] McNamara, Koelle and Gilman.[27]

Gradual loss of effect after continued use is a common factor in therapy with anticholinesterase compounds, with resistance developing as early as six months to DFP (Leopold and Cleveland),[28] and to Mintacol (Wessely, 1949).[29]

Chemical irritation is also frequent with organic phosphate compounds and results in conjunctival inflammation, which requires discontinuing the drug. This was especially notable with TEPP (Grant, 1947).[19]

Some properties of cholinesterase

Cholinesterase is an enzyme, generally present in living tissue, which acts as a catalyst in the hydrolysis of acetylcholine into choline and acetic acid. It was first demonstrated by Loewi in 1921.[3] Stedman, Stedman and Easson[30] in 1932 suspected that several types were present when they first suggested the name. In the following years two types (at least) of cholinesterase were demonstrated in sera, and also that physostigmine, even in small amounts, inhibits at least one of these types (Stedman, Stedman and White, 1933);[31] Shaw (1935);[32] Easson and Stedman (1937).[33] In 1939, Goodman, Carlson and Gilman[34] first spoke of specific cholinesterase, which was almost completely inactivated by minute amounts of physostigmine, and of nonspecific cholinesterase, which was but little affected even by high concentrations of physostigmine.

In 1940, Allen and Hawes,[35] found that serum cholinesterase and red blood cell cholinesterase are not identical, in chemical study of human blood. A qualitative difference between serum cholinesterase and red blood cell cholinesterase was seen in relative actions on acetylcholine, as red blood cell cholinesterase showed maximum activity in low concentrations of acetylcholine. Red blood cell cholinesterase split acetyl-β-methylcholine at the same rate as acetylcholine, while acetylcholine was only slightly hydrolyzed by serum.

Mendel and Rudney (1943)[36] and also others, confirmed the above and showed that brain and red blood cell cholinesterase is specific, while serum cholinesterase was nonspecific and catalyzes the hydrolysis of noncholine esters also. Mendel, Mundell and Rudney (1943)[37] reported that only true cholinesterase hydrolyzes acetyl-8-methylcholine, while only pseudocholinesterase hydrolyzes benzylcholine. Thus there are two groups, specific cholinesterase in brain and nerve (Nachmansohn and Rothenberg, 1944-45);[38] retina (Francis, 1953);[39] nonspecific cholinesterase in blood serum and glands.

Cholinesterase activity in ocular tissues

Aqueous

No cholinesterase activity in the primary aqueous could be demonstrated in normal aqueous humor of horse or ox eye by Weve and Fischer,[40] Uvnas and Wolff,[41] and Jaffe.[42] If the eyes were allowed to remain in the refrigerator for up to six hours or if secondary aqueous were tested (first paracentesis discarded), some cholinesterase activity was found. These authors suggested that biologic barriers were broken down in postmortem changes, so that enzyme finds its way into the anterior chamber, and that partial emptying of the anterior chamber causes inflow of fluid from adjoining tissues.

No cholinesterase activity was found in rabbit aqueous by Plattner and Hintner,[43] and in normal cat and rabbit aqueous by Engelhart,[44] except that if the eyes were treated with physostigmine prior to aqueous puncture, some acetylcholinelike response was noted on using biologic assay methods.

Grosz and Goreczky[45] showed increased

TABLE 1

CHOLINESTERASE ACTIVITY IN THE EYE ON CORALOX

Normal Values: Iris and Ciliary Body	24 mg. ACh hydrolyzed/100 mg. wet tissue
Retina	144 mg. ACh hydrolyzed/100 mg. wet tissue

Percent Normal Cholinesterase Activity (3 animals)

Time (day)	Iris and Ciliary Body		Retina
	Treated Eye	Untreated Eye	
1	50	100	100
3	33	75	90
3	36	90	85
4	44	75	85
7	33	66	54
14	33	50	43
28	35	55	45

cholinesterase content of aqueous and Pletneva, et al.[46] observed by biologic assay an increased acetylcholinelike content in glaucomatous eyes of humans. DeRoetth[47] demonstrated specific cholinesterase in the aqueous of the ox, while he found nonspecific cholinesterase in the secondary aqueous of the cat.

Viikari[45] demonstrated in 1955 increased cholinesterase activity in aqueous, using biologic assay for acetylcholine action on leech muscle, and frog muscle preparations, after incubation of the aqueous, from eyes treated with polyalkylphosphates. He believed this was possibly due to increased permeability and diffusion into the eye. He also noted that Sugawara[49] reported similar studies.

IRIS AND CILIARY BODY

Cholinesterase activity in the iris and ciliary body of the rabbit was demonstrated by Bakker,[30] and Plattner and Hintner,[43] Parasympathetic activity in the cat and rabbit iris was reported by Engelhart,[44] and Velhagen[51] found similar results in the uveal extracts of rabbit, sheep and ox. Weve and Fischer[40] found activity in human choroid, subretinal fluid and retina.

DeRoetth[47] studied cholinesterase activity in ocular tissues by the colorimetric method of Hestrin[52] and correlated activity with the histology of the tissue, so that he was able to state that the muscle and nerve-containing tissues of the eye could be expected to show cholinesterase activity. He showed that the iris, ciliary body and serum of the rabbit; the iris, ciliary body, aqueous and vitreous of the ox; the iris of the horse; iris and ciliary body of the cat; and the retina of the dog, cat, rabbit, ox and horse, all demonstrated a hydrolysis pattern typical of that of specific cholinesterase. Nonspecific cholinesterase was observed in the ciliary body of the horse and in the serum and secondary aqueous of the cat. He proved that in the secondary aqueous of the cat, the cholinesterase is derived from the serum. In rabbit tissues, the iris was found to have an average of 28 acetylcholinesterase units (mg. acetylcholine hydrolyzed per gm. wet tissue per hour). The retina was found to have 130 units, and he found his values to compare with those of Nachmansohn for nerve tissue.[53]

AQUEOUS AFTER TREATMENT

No cholinesterase activity in aqueous after physostigmine and neostigmine was reported by Viikari[48] while polyalkylphosphates, including DFP, were associated with cholinesterase activity in the aqueous. Von Sallmann[54] could find no increase in acetylcholine concentration in the aqueous after DFP.

DeRoetth[47] reported that for maximal

miosis, a reduction of cholinesterase activity in the iris and ciliary body of the rabbit to 15 percent of normal was necessary. He stated that the conflict and confusion of results in the literature are based on different methods of analysis, and that inaccuracies are due to use of excess substrate. On the basis of his studies, cholinesterase activity could only be expected in muscle and nerve containing tissues, and error would result from attempting to search for the enzyme in tissues where it would not be expected.

Retina

High values for cholinesterase activity in the retina of dog and ox were reported by Nachmansohn[53] and parasympathetomimetic activity demonstrated by biologic methods by Velhagen[51] in the retina of rabbit, sheep and ox. Bakker[50] found similar results in rabbit retina.

Vascular effects

Anticholinesterase compounds cause vasodilatation and increased capillary permeability. Congestion of the iris and of the conjunctival vessels is most frequently found. Gittler[55] found no irritation or congestion of the conjunctival vessels following Mintacol. Congestion may appear as late as 48 hours after use, but as the eye becomes accustomed to the substance, these signs disappear. Atropine prevents the congestion (Marr and Grob, 1950).[56] Mintacol (TS-219) injected into the anterior chamber produced hyperemia, hemorrhages and fibrin exudation (Iserle and Rezek, 1951).[57]

Aqueous humor with an elevated protein level is found in the anterior chamber after DFP and TEPP (Swan and Hart, 1940;[58] Scholz, 1946;[26] von Sallmann and Dillion, 1947;[59] Aldrige, Davson, Dunphy and Uhde, 1947).[60] Normal protein content of the rabbit aqueous is 40 mg. per 100 ml. (Adler, 1953);[61] von Sallmann and Dillon, 1947;[59] and Miller and Swanjlung[63] showed with experiments with fluorescein, inulin and other substances that anticholinesterase drugs increase vascular permeability. Leopold, (1951)[64] was unable to demonstrate any change in calibre of ciliary vessels. Von Sallmann and Moore (1948)[65] fractionated aqueous humor and found that the protein has the same electric field mobilities as plasma protein, and thus was presumably derived from blood and also contained hyaluronic acid, alone or in complex.

The A/G ratio is higher in aqueous humor than in blood and contains albumin, and α, β and γ globulin as well as fibrinogen (Wittner, 1952).[66] Recent microfractionation of aqueous proteins by various methods were reported by Remky[67] and D'Ermo.[68]

Deleterious effects on the tissues of the eye were not found after use of DFP and TEPP, and studies on these effects were made by Grant (1948),[19] and Leopold and Comroe (1946).[21] Epithelial blebs or cysts on iris and ciliary body have been reported with DFP (Scholz, 1946),[26] and with phospholine (Krishna and Leopold)[69] in adults. Miller[70] reported less incidence of cysts with phospholine than with DFP in children.

Retinal detachment has been reported and may be produced by the strong forward pull of ciliary muscle contraction by DFP (Marr, 1947;[71] Scheie, 1949);[72] by phospholine, Becker, 1959).[14] Gradle and Snydacker[73] reported detachment of the retina with use of physostigmine and pilocarpine in 1940.

Production of angle closure in predisposed eyes through use of polyalkylphosphates generally limits this use of these compounds.

Regeneration of cholinesterase activity

Wilson, Ginsberg and Meislich[74] studied the reactivation of acetylcholinesterase inhibited by TEPP and DFP. They described the enzyme as having two active sites, an esteratic and an anionic site, and that an acetyl enzyme complex is formed with esters. Water breaks down the complex and produces the active enzyme with activity of

the speed of hydrolysis. Alkylphosphates combine with the enzyme to form a phosphoryl enzyme complex which does not react with water, or reacts at a rate one-sixtieth of the normal, even though the anionic site is free. Reactivation or reversal of this inhibition occurs slowly in water, and more rapidly with choline, hydroxamic acids and oximes.

Kewitz and Nachmansohn[5] found that 2-PAM reversed the cholinergic effects of diethyl and di-isopropyl organic phosphates, and found values as low as two percent of normal cholinesterase activity in brain tissues of animals treated simultaneously with DFP and 2-PAM.

DeRoetth described cholinesterase activity as recovering sharply, parabolically, to 50 percent of normal in one week, following the inhibition produced by the instillation of one drop of 0.1-percent DFP in the eyes of rabbits, but full recovery to normal levels required 47 days.

Methods

Co-Ral or coralox was instilled into the right eye of albino rabbits weighing between 2.0 and 3.0 kg. in 0.25-percent concentration in peanut oil on a three-times-daily schedule for periods of up to one month. Chemical studies of cholinesterase activity were carried out on samples of aqueous humor, iris and ciliary body and retina. Tissue samples from the brain, salivary gland and ileum were taken. Blood cholinesterase was studied in heparinized samples, divided into serum and washed red blood cells in 50-percent concentration.

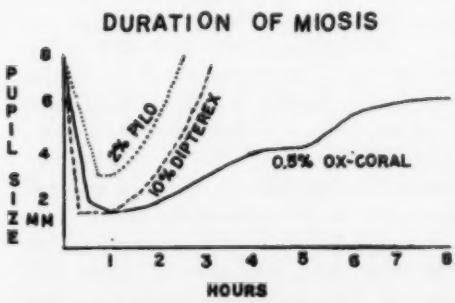


Fig. 2 (Kadin). Effect as a miotic in rabbits.

Two methods of cholinesterase assay were employed: (1) manometric method of DuBois and Mangun,[10] and (2) the chemical method of Hestrin,[52] which uses the reaction of alkaline hydroxylamine with acetylochine to form hydroxamic acid as a method of assay.

Technique

Blood was drawn in heparinized syringes, and then the animals were killed by injecting 10 ml. of air into an ear vein. It was found that this produced a marked opisthotonus, and that, if the head of the animal were maintained in the elevated position, essentially bloodless eyes were obtained in most cases. The aqueous humor was immediately withdrawn by anterior chamber puncture, and then the eyes were dissected to remove the iris and ciliary body in one piece, since it was found impossible to separate them anatomically,[71] and samples of retina were stripped off. Samples of brain, ileum and salivary gland were then removed. (This material will be reported separately.)

All tissues were washed in distilled water for at least one hour, blotted and weighed wet. Glass homogenizers were used to make a 10 percent homogenate in phosphate buffer, pH 7.2. Aliquot portions were taken for both types of analysis. Acetylcholine chloride 5.4 mg. per 3.0 cc. flask system was used for the manometric substrate, and 2.0 mg. per ml. of acetylcholine base was used to prepare a standard curve for acetylcholine in the colorimetric determination. Tissues were incubated at 38°C. for 30 minutes in a shaking water bath. Acetylcholine hydrolyzed was determined at 500 mu in the Beckman DU spectrophotometer, using 10-percent $FeCl_3$ solution for color. The sensitivity of the manometric and chemical methods is such that less than 50 micrograms of acetylcholine cannot be measured.[47] Tissue

blanks were prepared for each sample. Only one sample of aqueous humor was taken from any eye and represents primary aqueous.

It was found that determinations by either method could be compared by calculation, based on mole-for-mole reactions of the enzyme with acetylocholine. Kewitz[5] found higher values for cholinesterase activity by using a chloroform method of extraction of tissues in the first 24 hours after use of anticholinesterase compounds, and recommended use of the colorimetric method for values below 10 percent of normal. Values obtained were comparable with those of De-Roetth[47a] and Kewitz and Nachmansohn.[5]

Results

No cholinesterase activity was found in normal primary aqueous humor of rabbits by either method of determination (table 2). In rabbit eyes treated with Co-Ral or coralox, the aqueous was found to contain a protein material, which precipitated on treating with acid or heating, to produce a milky clouding. Treatment of normal aqueous with alkaline hydroxylamine as for acetylcholine determination produced no color change with ferric chloride, but primary aqueous humor from coralox treated eyes contained material which did react with hydroxylamine to produce a color change. This effect was found also if the aqueous was heated prior to chemical treatment. Hestrin[52] reported that hydroxylamine in vitro reacts with many esters, aldehydes and O-acyl derivatives as well as ammonium hydroxide to form oximes or hydroxamic acid. He found that peanut oil and ascorbic acid did not produce a ferric color change with his method. Coralox did not produce this reaction. If calculations were made on the amount of color change produced, assuming that this material is a protein containing such chemical groups, then approximately 750 mg. per 100 ml. aqueous was determined as protein material. Total protein determinations by the Nessler method averaged 445 mg. percent for untreated eyes and 712.8 for treated eyes. In untreated eyes, this is presumed to be due to systemic absorption.

TABLE 2

AQUEOUS CHOLINESTERASE AS UNCORRECTED READINGS OF MG. OF ACETYLCHOLINE HYDROLYZED PER 0.2 ML. AQUEOUS

	Right	Left
Normal eyes	0	0
(5 animals)	0	0
Postmortem		
(4 animals)	0.18	0.14
	0.16	0.17
Coralox treated		
16 hr.	0.16	0.0
20 hr.	0.08	0.04
3 da. (2)	0.17	0.02
5 da.	0.30	0.07
10 da.	0.38	0.18
14 da.	0.46	0.34
28 da.	0.12	0.04
Manometric Determinations (cmm. CO_2 Liberated per 0.2 ml. aqueous per 30 minutes)		
Normal eyes	0	4.0
	0	4.6
	7.0	
	10.0	
	0	
	6.36	
Coralox	37.3	
	22.26	17.76
10 da. after	15.0	20.86
14 da. after	25.27	8.94
CoRal	10.79	10.51
	33.39	17.84
	33.13	17.88

It was found that some cholinesterase activity was present in aqueous humor of Co-Ral and coralox treated eyes. Aqueous humor from the control or untreated eye of the same rabbit on extended treatment with Co-Ral or coralox also was found to contain some cholinesterase activity. Protein material was found to be present in the aqueous humor of these eyes also. It could be inferred that this was the result of systemic absorption of coralox and Co-Ral.

Aqueous humor from the eyes of rabbits that were dead over one-half hour was found to show some cholinesterase activity. This is attributed to post-mortem changes

permitting diffusion of this material into the anterior chamber.

In the iris and ciliary body, inhibition of cholinesterase activity to low levels (15 percent) was found in treated eyes. It was found that on chronic administration of 30 days' duration, that inhibition persisted as long as two weeks after cessation of treatment. At this level of dosage, inhibition of cholinesterase activity in iris and ciliary body and retina occurred to levels as low as 50 percent of normal.

Following instillation of oil eyedrops in the rabbit, the oil could be found in the bronchi and lung spaces of the rabbit, by gross dye or fluorescein stain methods, so that effective systemic absorption in the rabbit occurs in the lung, as well as on the nasal mucosa and conjunctiva.

Summary

Coralox is an organic polyalkylphosphate anticholinesterase compound which is related to TEPP and the Russian compound A2. It has the ability to produce maximal miosis in rabbit eyes lasting four hours, and up to 15 hours in humans. With coralox, or Co-Ral, some cholinesterase activity is found in primary aqueous humor of treated rabbit eyes with lesser activity in control eyes, and this occurs with the finding of a protein material in the aqueous, at least the majority of which is capable of reacting with alkaline hydroxylamine. Reduction of cholinesterase activity in the iris and ciliary body of treated eyes occurred to levels as low as 15 percent of normal, and in the iris, ciliary body, and retina of control or untreated eyes to levels of 50 percent of normal. Effects of this compound on other tissues and blood, as well as clinical use for the treatment of glaucoma will be reported in subsequent communications.

Evidence that the sulfur analogue of this compound is capable of producing the finding of increased protein levels in the aqueous humor of the rabbit eye, by direct absorption or instillation, or by systemic absorption, is probably not unique, but represents the effect of vasodilatation which is a general characteristic of these compounds.

950 East 59th Street (37).

Acknowledgment

I am indebted to Kenneth P. DuBois, Ph.D., professor of pharmacology, and to Frank W. Newell, M.D., professor of ophthalmology at the University of Chicago, for their sponsorship, preceptorship and aid in the furthering of this work, which was supported by grant BT-449, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

References

1. DuBois, K. P.: Insecticides, rodenticides, herbicides; household hazards. Postgrad. Med., **24**:000 (Sept.) 1958.
2. DuBois, K. P., Schmalgemeier, D., and Plzak, G.: To be published.
3. Loewi, O.: Ueber humorale uebertragbarkeit des herz nervenwirkung Arch. Ges. Physiol., **189**:239, 1921.
4. Mano, J. G., and Leopold, I. H.: Evaluation and use of oximes in ophthalmology. Am. J. Ophth., **46**:724, 1958.
5. Kewitz, H., and Nachmansohn, D.: A specific antidote against lethal alkyl phosphate intoxication; III. Repair in intracranial lesion; IV. Effects in brain. Arch. Biochem. & Biophys., **66**:271, 1957.
6. Quoted from Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics. New York, MacMillan, 1958.
7. Lange, W., and Krueger, G. V.: Ueber ester der monofluorphosphorsaure. Ber. d. deutsch. chem. ges., **65**:1598, 1932.
8. McCombie, H., and Saunders, B. C.: Alkyl fluorophosphonates: preparation and physiological properties. Nature, London, **157**:287, 1946.
9. Schrader, G.: Die entwicklung neuer insektizide auf grundlage organischer Fluor- und phosphoroverbindungen. Angew. Chem., **62**:471, 1950.
10. DuBois, K. P., and Mangun, G. H.: Effect of hexaethyl tetraphosphate on cholinesterase in vitro and in vivo. Proc. Soc. Exper. Biol. & Med., **64**:137, 1947.
11. Koelle, G. B., and Steiner, E. C.: The cerebral distribution of a tertiary and quaternary anti-

cholinesterase agent following intravenous and intraventricular injection. J. Pharmacol. & Exper. Therap., **118**:420, 1956.

12. Schaumann, W., and Job. C.: Differential effects of a quaternary cholinesterase inhibitor, phospholine, and its tertiary analogue, compound 217-AO, on central control of respiration and on neuromuscular transmission. The antagonism of 217-AO of the respiratory arrest caused by morphine. J. Pharmacol. & Exper. Therap., **123**:114, 1958.

13. Leopold, I. H., Gold, P., and Gold, D.: Use of a thiophosphinyl quaternary compound (217MI) in treatment of glaucoma. A.M.A. Arch. Ophth., **58**:363, 1957.

14. Becker, B., Pyle, G. C., and Drews, R. C.: Tonographic effects of echothiophate iodide: reversal by 2-PAM. Am. J. Ophth., **47**:635, 1959.

15. Gittler, R., and Pillat, B.: Die verwendung von dekamethylenbis-N-methylcabaminoyl-m-trimethylammoniumphenol (BC-48) bei der therapie des glaukoms. Arch. f. Ophth., **157**:473, 1956.

16. Miller, H. A., Divert, J., and Crouzet, J.: Decamethylene bis-neostigmine (BC48) in treatment of ocular hypertension. Bull et mem. Soc. franc. d'ophth., **70**:518, 1957.

17. Ustimenko, L. L.: Soviet miotic preparation tetraethylmonophrophosphate (A2) in glaucoma. Vestnik oftal., **2**:11, 1956.

18. Koelle, G. B., and Gilman, A.: Anticholinesterase drugs. Pharmacol. Rev., **1**:166, 1949.

19. Grant, W. M.: Miotic and antiglaucomatous activity of TEPP in human eyes. A.M.A. Arch. Ophth., **39**:579, 1948.

20. Sugar, H. S.: The Glaucomas. London, Kimpton, 1951.

21. Leopold, I. H., and Comroe, J. H., Jr.: Use of DFP in the treatment of glaucoma. A.M.A. Arch. Ophth., **36**:1, 1946.

22. Abraham, S. V.: Special reactions to the miotic fluoropryl. Am. J. Ophth., **36**:1122, 1953.

23. Marr, W. G., and Grob, D.: Some ocular effects of a new anticholinesterase agent, TEPP. Am. J. Ophth., **33**:904, 1950.

24. Rosengren, B.: Quoted from Viikari, K. (Ref. 48) Svenska lakartidn., **40**:1563, 1943.

25. Wheeler, J. R.: Quoted in Excerpta Med. Section XII, **5**:175, 1951.

26. Scholz, R. O.: Studies on the ocular reactions of rabbits to DFP. J. Pharmacol. & Exper. Therap., **88**:23, 1946.

27. McNamara, B. P., Koelle, G. B., and Gilman, A.: Treatment of DFP poisoning in rabbits. J. Pharmacol. & Exper. Therap., **88**:27, 1946.

28. Leopold, I. H., and Cleveland, A. F.: DFP in chronic wide-angle glaucoma. Am. J. Ophth., **36**:226, 1953.

29. Wessely, K.: Zum problem der augewöhnung au örtliche reize und medikamente. Zentralbl. f. d. ges. ophth., **51**:119, 1949.

30. Stedman, E., Stedman, E., and Easson, L.: Cholinesterase: an enzyme present in the blood serum of the horse. Biochem. J., **26B**:2056, 1932.

31. Stedman, E., Stedman, E., and White, A. O.: Comparison of cholinesterase activities of blood sera from various species. Biochem. J., **27**:1055, 1933.

32. Shaw, F. H.: Formation of acetylcholine in the body and investigation of cholinesterase. Austral. J. Exper. Biol. & M. Sc., **13**:251, 1935.

33. Easson, L. H., and Stedman, E.: Specificity of cholinesterase. Biochem. J., **31**:1723, 1937.

34. Goodman, L. S., Carlson, R. I., and Gilman, A.: Muscle and blood cholinesterase in myasthenia gravis, case study. J. Pharmacol. & Exper. Therap., **66**:15, 1939.

35. Allen, G. A., and Hawes, R. C.: Cholinesterase in blood of allergic patients. J. Biol. Chem., **133**:375, 1940.

36. Mendel, B., and Rudney, H.: Studies on cholinesterase; cholinesterase and pseudocholinesterase. Biochem. J., **37**:59, 1943a.

37. Mendel, B., Mundell, D. B., and Rudney, H.: True and pseudocholinesterase. Biochem. J., **37**:473, 1943.

38. Nachmansohn, D., and Rothenberg, M. A.: On the specificity of cholinesterase in nervous tissue. J. Biol. Chem., **158**:653, 1945.

39. Francis, C. M.: Cholinesterase in retina. J. Physiol., **120**:435, 1953.

40. Weve, H. J. M., and Fischer, F.: Ueber den azetylcholinesterase gehalt der subrethalen flüssigkeit bei reupturellen Netzhautablösungen. Ophthalmologica, **96**:348, 1939.

41. Uvnas, B., and Wolff, H.: On the occurrence of acetylcholine in aqueous humour and vitreous body. Acta Ophth., **16**:157, 1938.

42. Jaffe, N.: Cholinesterase in the aqueous humour of the eye. A.M.A. Arch. Ophth., **40**:273 (Sept.) 1948.

43. Plattner, F., and Hintner, H.: Die Spaltung von Azetylcholine durch organextrakte und Körperflussigkeiten. Arch. f.d. ges. Physiol., **225**:19, 1930.

44. Engelhart, E.: Der humerale wirkungsmechanismus der oculomotorius-reizung. Arch. f.d. ges. Physiol., **227**:220, 1931.

45. Grosz, T., and Gorecsky, L.: Adatok a primaer glaucoma pathogenesisekez. Budapest, Szemeszeti Tanulmanyok, 1948.

46. Pletvana, N. A., Raeva, N. V., and Voronina, E. G.: Biologische Analyse der Flussigkeit aus der Vorderkammer der glaucomatosen Kranken. Vestnik, oftal., **13**:462, 1938; Abstracted, Zentralbl. f.d. ges. Ophth., **43**:693, 1939.

47a. DeRoetth, A., Jr.: Cholinesterase activity in ocular tissue and fluids. A.M.A. Arch. Ophth., **43**: 1104, 1950.

47b. ———. Further study on cholinesterase activity in ocular tissues. Am. J. Ophth., **34**:120, 1951.

48. Viikari, K.: Studies of cholinesterase activity in aqueous humour of man and some animals. Ann. Med. Exper. & Biol. Fenn., **33**: (Supp. 4) 1955.

49. Sugawara, K.: Acta Soc. Ophth. Jap., **57**:744, 1953. Quoted from Viikari, K. (Ref. 48)

50a. Bakker, A.: Beitrage zur kenntnise einiger merkwurdiger pupillen bewegungen. Arch. f. Ophth., **139**:273, 1938.

50b. ———: Ueber acetylcholinbildung in der retina. Arch. f. Ophth., **141**:326, 1939.

51. Velhagen, K.: Neue Untersuchungen über aktiv Stoffe im auge. Arch. f. Augenh., **109**:195, 1936.

52. Hestrin, S.: The reaction of acetylcholine and other carboxylic acid derivatives with hydroxylamine and its analytical application. J. Biol. Chem., **180**:249, 1949.

53. Nachmansohn, D.: Distinction between acetylcholine and other choline ester splitting enzymes. Science, **110**:98, 1949.

54. Sallmann, L., von: Quoted by Stone, W. C.: Use of DFP in the treatment of glaucoma. A.M.A. Arch. Ophth., **43**:36, 1950.

55. Gittler, R.: Experiments with Mintacoli. Wien klin. Wchnschr., **62**:379, 1950.

56. Marr, W. G., and Grob, D.: Some ocular effects of a new acetylcholinesterase agent (TEPP). Am. J. Ophth., **33**:904, 1950.

57. Iserle and Rezek: Quoted in Ophth. Lit., **5**:790, 1951. Ceskoslov. Ofth., **7**:174, 1951.

58. Swan, K. C., and Hart, W. M.: A comparative study of the effects of mecholyl, doryl, eserine, pilocarpine, atropine and epinephrine on blood-aqueous barrier. Am. J. Ophth., **23**:1311, 1940.

59. Sallmann, L. von., and Dillion, B.: Effect of DFP on rabbit eyes: On the capillaries of the anterior segment. Am. J. Ophth., **30**:1244, 1947.

60. Aldridge, W. H., Davson, H., Dunphy, E. B., and Uhde, G. I.: The effects of DFP vapor on the eye. Am. J. Ophth., **30**:1405, 1947.

61. Adler, F. H.: Physiology of the Eye. London, Kimpton, 1953.

62. Wessely, K.: Auge und tonuslage im vegetativen nervensystem. Munchen. med. Wchnschr., **95**:43, 1953.

63. Miller, S. J. H., and Swanjlung, H.: Appearance of fluorescin in glaucomatous eyes. Brit. J. Ophth., **35**:356, 1951.

64. Leopold, I. H.: Pharmacology and toxicology. A.M.A. Arch. Ophth., **46**:212, 1951.

65. Sallmann, L. von., and Moore, D. H.: (1948) Quoted from Davson, H.: Physiology of the Ocular and Cerebrospinal Fluid. Boston, Little, Brown, 1956.

66. Wittner: Quoted from Davson (Ref. 65). Elektrophorese des Kammerwassers. Ophthalmologica, Basel, **123**:280, 1952.

67. Remky, H.: Eine mikromethode zur eiweissbestimmung in Kammerwasser. Docum. Ophth., **11**:113, 1957.

68. D'Ermo, F.: Die technik der papier mikrolektrophorese zur fractionierten Bestimmung der Proteine in kleine menge normalen Kammerwasser. Docum. Ophth., **11**:116, 1957.

69. Krishna, N., and Leopold, I. H.: Phospholine Iodide or echothiophate (217MI) in treatment of glaucoma. Further observations. A.M.A. Arch. Ophth., **62**:166-300, 1959.

70. Miller, J. E.: Read at a meeting of the Ophthalmology Section, A.M.A. Convention, June, 1959.

71. Marr, W. G.: Clinical use of DFP in chronic glaucoma. Am. J. Ophth., **30**:1423, 1947.

72. Scheie, H. G.: Treatment of primary glaucoma by medical means. Tr. Am. Acad. Ophth., **53**:186, 1949.

73. Gradle, H. S., and Snydacker, D.: Retinal detachment occurring in primary compensated glaucoma. Am. J. Ophth., **23**:52, 1940.

74. Wilson, J. B., Ginsberg, S., and Meislich, E. K.: The reactivation of acetylcholinesterase inhibited by TEPP and DFP. J. Am. Chem. Soc., **77**:4286, 1955.

STUDIES ON ANTIBODY PRODUCTION IN RABBIT EYES*

I. Antibody formation in vitro after intraocular injection of typhoid bacilli

Michael I. Wolkowicz, M.D., Joseph W. Hallett, M.D. and Irving H. Leopold, M.D.
(With the technical assistance of Busja Shinar)
Philadelphia, Pennsylvania

A clearer comprehension of intraocular forces of resistance to infections and allergic insults should result from the study of intraocular antibody formation.

In experimental leptospiral and tuberculous uveitis Witmer[1-3] demonstrated a higher antibody titer in the aqueous than in the blood serum, if the eye was the primary focus of infection. By paper electrophoresis he calculated the antibody activity per gram of globulin and computed the true titer ratio of aqueous to blood serum.[4] Thompson and Olsen[5] demonstrated local antibody formation in the rabbit cornea, and at times in other ocular tissues, before appearing in the general circulation. Wolkowicz, Hallett and Leopold,[6] after intraocular injection of antigen, found Cx-reactive protein antibody in rabbit aqueous before it appeared in the general circulation.

These data raise such questions as:

1. Can local antibody titer mean excessive seepage from the general circulation?

2. Can local higher concentration of antigen attract antibody-producing cells from elsewhere?

3. How and in what tissues or cells are antibodies formed?

Some answers have recently been provided by Fagraeus,[7,8] Coons,[9] Leduc,[10] McMaster,[11] Thorbecke,[12] Kenning[13] and their coworkers, to mention only a few. They demonstrated antibody formation in tissue culture as a function of the reticulo-endothelial system. The role of immature plasma cells in antibody production was ably described by Coons[14] with the use of his fluorescein conjugation technique. Michaelides[15] produced antibodies in tissue culture by adding the antigen to the nutrient fluid. Similarly our studies reported in this paper deal with antibody formation by uveal components in tissue culture.

Materials and Methods

Adult rabbits of average weight (4.5-5.5 lbs.) were used. The antigen was killed typhoid bacilli. Stock typhoid-paratyphoid vaccine, 100 million organisms per cc. and typhoid-H bacilli in 100, 200 and 300 million organisms per cc. were used. The suspension fluid was either saline solution or a modified White[16] adjuvant emulsion to which killed tubercle bacilli were added.

The dose of antigen was 0.05 to 0.1 cc. injected through a 26-gauge needle. The eyes to be injected received several applications of Neosporin® ointment during the preceding 24 hours. The injections were given intracamerally, intravitreally by the Foss[17] method or subretinally as described by Vogel.[18] One week later some of the eyes were enucleated, the rest received a second intraocular injection in the same fashion as the first one and were enucleated four or five days later when the antibody titer, according to Fagraeus,[7] is at its peak. The right eye of each rabbit received the antigen, the left eye served as control, either remaining intact or being injected with the suspension fluid alone. Where adjuvant emulsion was used, the killed tubercle bacilli were omitted in the control injections.

Immediately after enucleation half the

* From the Department of Research, Wills Eye Hospital. This study was supported in part by a grant from the National Institutes of Health (BE-1062(C)2, and by the Hartford Foundation Grant.

globe was fixed in formalin for histologic preparation and the other half was placed in water where the uvea could be teased from the retina and sclera with greater ease. This half of the uvea was further divided into two parts, one part comprising choroid, ciliary body and iris, the other was cut into its three anatomic components.

The four separate bits of tissue from each eye were placed in a tube of culture medium containing three parts of normal rabbit serum, two parts of Tyrode solution with four times its normal glucose content and one part of isotonic sodium bicarbonate solution penicillin; streptomycin and nystatin were each added to a concentration of 100 units/cc. of medium. A mixture of 80-percent oxygen, 4.5-percent carbon dioxide and the remainder nitrogen was gassed through the nutrient fluid for 20 to 30 seconds. The tubes containing the tissue fragments were kept in the incubator and the fluid was tested for antibody activity at regular intervals by the standard agglutination method.

The eyes injected once had 0.2 cc. of antigen added to their cultures either immediately, six hours or 17 hours later. A few of these eyes showed antibody activity without added antigen and were given no further antigenic stimulus.

One day after the test for antibodies, the uveal fragment was gently removed from its tube, rinsed in saline solution at room temperature, placed in a fresh nutrient fluid and gassed as previously. After negative culture for two successive days the tissue was triturated and the tissue juice tested for antibodies, which were unable to seep into the culture media. Thompson's[5] work prompted us to triturate all the corneas and to test the tissue extract for antibodies; the results were uniformly negative and are omitted from our following tabulations.

Results

In the first phase of our work, the stock mixed typhoid-paratyphoid suspension was used. Two antigen injections were administered intravitreally in the right eye at weekly intervals (table 1). All the blood sera showed a high titer of 1/160 or 1/320. Only one aqueous had a positive agglutination test. Interestingly enough, this is also the only eye in this series where the iris gave a positive response with a titer of 1/80. Also in the same eye one of the uveal components, namely the ciliary body, continued to discharge agglutinins for three consecutive days. In all the other eyes the antibodies could be detected only in the first culture tube. A consistently positive component in this series was the choroid (one exception: rabbit 499). In the rabbit No. 424 where the choroidal titer is 1/80 and the "total uvea" titer is 1/20 one can assume that the choroid was the sole component discharging antibodies (fig. 1).

TABLE 1

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO INTRAVITREAL ANTIGEN INJECTIONS

Material	Rabbit 423		Rabbit 424		Rabbit 425		Rabbit 513		Rabbit 469		Rabbit 499	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/160	—	1/160	—	1/320	—	1/320	—	1/160	—	1/160	—
Aqueous	0	—	0	—	1/20	—	0	—	0	—	0	—
Total uvea	1/20	24	1/20	24	1/40	24	1/20	24	1/20	24	1/20	24
Choroid	1/20	24	1/80	24	1/80	24	1/20	24	1/20	24	0	0
Ciliary body	0	0	0	0	1/40	72	0	0	1/20	24	0	0
Iris	0	0	0	0	1/80	24	0	0	0	0	0	0

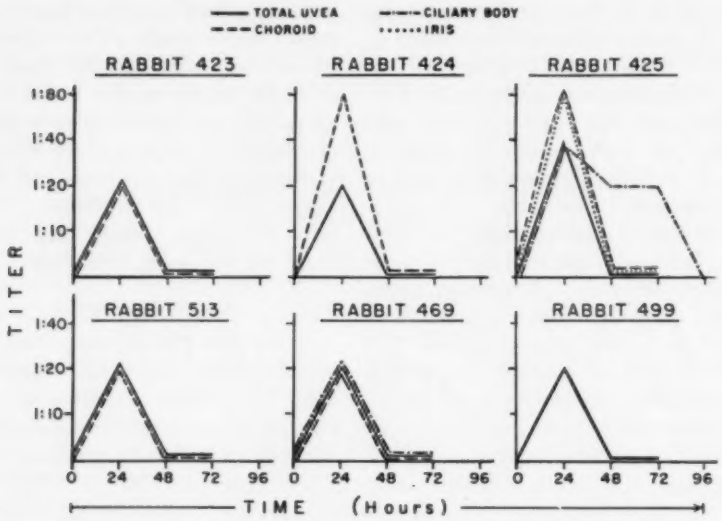


Fig. 1 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following two intravitreal antigen injections.

In the second part two antigenic injections were deposited in the anterior chamber (table 2). Here again the blood serum showed in all four rabbits, a high titer of 1/160+ and 1/320+. Two of the four rabbits had a positive aqueous reaction. In spite of this all the iris cultures were consistently negative. The overall titers were low, only two "choroid" media and one "ciliary body" media were positive. None of the cultures were positive after the second day (fig. 2).

The third part of this work was divided in two subgroups. In the first lot the primary antigen injection was administered intravitreally and the booster dose was added to the nutrient fluid (table 3). In the second lot the booster dose was also added in vitro but the primary injection was given in the anterior chamber (table 4). In the first subgroup the titer in the blood serum was uniformly high but all culture media were consistently negative. In the second subgroup one eye showed a positive response of all the uveal components following the booster dose and the "total uvea" continued to yield agglutinins 48 hours after the onset of incubation (Fig. 3).

The last part dealt with rabbit eyes sub-

TABLE 2

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO ANTIGEN INJECTIONS IN THE ANTERIOR CHAMBER

Material	Rabbit 483		Rabbit 485		Rabbit 488		Rabbit 489	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/160	—	1/320	—	1/320	—	1/320	—
Aqueous	0	—	0	—	1/20	—	1/40	—
Total uvea	1/20	24	1/20	24	1/20	24	1/20	24
Choroid	0	0	1/20	24	0	0	1/40	24
Ciliary body	0	0	0	0	0	0	1/20	24
Iris	0	0	0	0	0	0	0	0

TABLE 3

ANTIGEN TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING ONE INTRAVITREAL ANTIGEN INJECTION AND BOOSTER DOSE ADDED TO THE NUTRIENT FLUID

Material	Rabbit 432		Rabbit 437		Rabbit 440		Rabbit 446	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/80	—	1/320	—	1/320	—	1/320	—
Aqueous	0	—	0	—	0	—	0	—
Total uvea	0	0	0	0	0	0	0	0
Choroid	0	0	0	0	0	0	0	0
Ciliary body	0	0	0	0	0	0	0	0
Iris	0	0	0	0	0	0	0	0

TABLE 4

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING ONE ANTIGEN INJECTION IN THE ANTERIOR CHAMBER AND BOOSTER DOSE ADDED TO THE NUTRIENT FLUID

Material	Rabbit 450		Rabbit 452		Rabbit 453		Rabbit 457	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/160	—	1/320	—	1/320	—	1/320	—
Aqueous	0	—	0	—	0	—	0	—
Total uvea	0	0	0	0	0	0	1/80	48
Choroid	0	0	0	0	0	0	1/40	24
Ciliary body	0	0	0	0	0	0	1/40	24
Iris	0	0	0	0	0	0	1/40	24

mitted to subretinal antigen injections. Two eyes were injected with saline suspension of triple typhoid and two with typhoid vaccine suspended in an adjuvant emulsion with added killed tubercle bacilli for the purpose of producing a local granuloma (tables 5 and 6). Here again the antibody in the blood sera reached high levels. It is interesting to note that a positive aqueous response was elicited only in those eyes which were subjected to the suspension in adjuvant emulsion.

This might be in line with the experimental findings of White, et al.[16] A local granuloma, produced by suspension of egg albumin in emulsion adjuvant containing the wax fraction of mycobacterium tuberculosis was composed mainly of macrophages and epithelioid cells devoid of antibody activity.

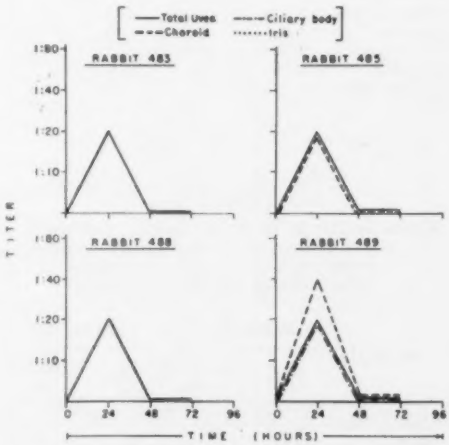


Fig. 2 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following two antigen injections in the anterior chamber.

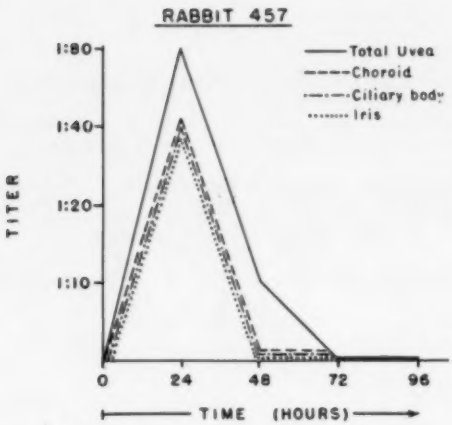


Fig. 3 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following one antigen injection in the anterior chamber and booster dose added to the nutrient fluid.

TABLE 5

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO SUBRETINAL INJECTIONS OF ANTIGEN SUSPENDED IN SALINE SOLUTION

Material	Rabbit 430		Rabbit 459	
	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/320	—	1/80	—
Aqueous	0	—	0	—
Total uvea	1/20	24	1/20	24
Choroid	1/40	48	0	0
Ciliary body	0	0	0	0
Iris	0	0	0	0

TABLE 6

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO SUBRETINAL INJECTIONS OF ANTIGEN SUSPENDED IN EMULSION ADJUVANT

Material	Rabbit 428		Rabbit 526	
	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/320	—	1/320	—
Aqueous	1/20	—	1/20	—
Total uvea	1/20	24	1/20	48
Choroid	0	0	1/20	24
Ciliary body	0	0	1/20	24
Iris	0	0	0	0

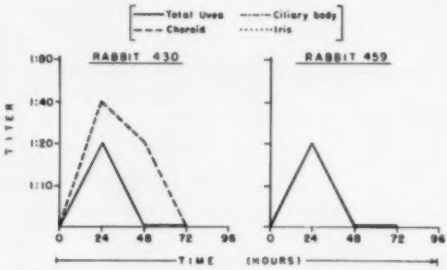


Fig. 4 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following two subretinal injections of antigen suspended in saline solution.

The plasma cells with antibody potential reached their greatest height in remote glands.

The circumstances in our experiments are somewhat different but the appearance of antibody in the aqueous might well be the result of a similar mechanism. Further histologic studies will be needed to confirm this statement (figs. 4 and 5). All the control eyes in this series showed no antibody activity and were therefore omitted in the tabulations. Once the culture media became negative for antibodies there was no further yield following the breaking up of the cell structure (trituration).

In an effort to increase the productivity of antibodies we concentrated the standard mixed typhoid vaccine by centrifugation: a five-cc. vial was reduced to one cc. of which 0.2 cc. was used for injection. The anterior

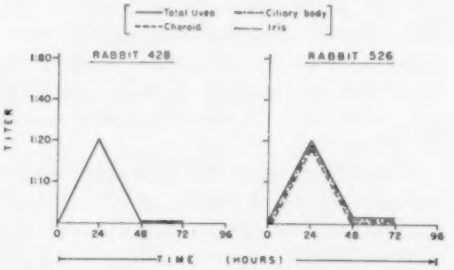


Fig. 5 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following two subretinal injections of antigen suspended in emulsion adjuvant.

TABLE 7

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO CONCENTRATED ANTIGEN INJECTIONS IN THE ANTERIOR CHAMBER

Material	Rabbit 548				Rabbit 552				Rabbit 553			
	O.D.		O.S.		O.D.		O.S.		O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/80	—	1/80	—	1/640	—	1/640	—	1/320	—	1/320	—
Aqueous	0	—	0	—	1/160	—	0	—	1/160	—	0	—
Total uvea	1/80	60	1/80	86	1/80	48	1/40	66	1/80	72	1/20	41
Formalin-treated uvea	0	—	0	—	0	—	1/20	24	0	—	0	—
Choroid	1/40	86	1/80	86	1/40	41	1/10	41	1/20	41	1/20	41
Ciliary body	1/40	86	1/40	86	1/40	48	1/20	41	1/10	24	1/10	24
Iris	1/40	86	1/40	86	1/20	48	0	—	1/20	24	1/10	24

chamber route was elected for this part of our experiments. The left eye which was the control eye was enucleated for uveal tissue culture, but remained undisturbed during the inoculation period. Another innovation was the treatment of "total uvea" fragment with four-percent formalin prior to the culture. This was done in order to find out how much of the antibodies was deposited in the uvea and how much was being produced by either autochthonous or migrated cells. Formalin ought to destroy all or most of the living cells but should not disturb the antibodies.

Table 7 illustrates the overall response to the highly concentrated antigen. The blood serum titer was high but so was the aqueous titer in two out of three rabbits. The tissue response was more prolonged involving all the uveal components. Unexpected also was a similar antibody response of the control eye. In fact, it is the formalin treated uvea of the left eye which showed traces of antibodies for 24 hours after incubation. Figure 6 shows the over-all similarity between the tracings of the inoculated and control eye.

In the second phase of this study we used typhoid-H exclusively. The standard concentration for the ensuing experiments was 100 million organisms per cc. Two injections in the anterior chamber at weekly intervals produced a low blood serum titer in one rabbit and no antibodies in the serum of the second rabbit (table 8). The aqueous reaction was negative but the tissue reaction was widespread, vigorous and prolonged. Titers of 1/320 were found in the choroid containing cultures. Antibodies were present in all the formalin treated uveas. Figure

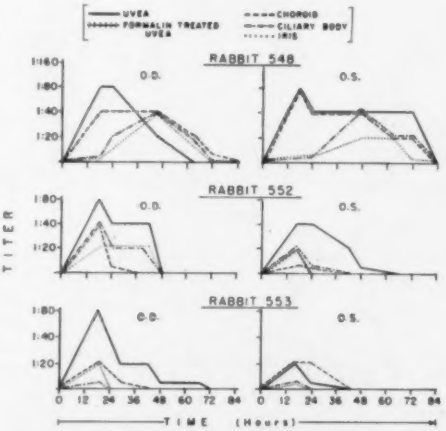


Fig. 6 (Wolkowicz, et al.). Uveal antibody activity in tissue culture following two concentrated antigen injections in the anterior chamber.

TABLE 8

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO INJECTIONS OF TYPHOID-H (100 MILLION PER CC.) IN THE ANTERIOR CHAMBER

Material	Rabbit 556				Rabbit 557			
	O.D.		O.S.		O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/40	—	1/40	—	0	—	0	—
Aqueous	0	—	0	—	0	—	0	—
Total uvea	1/160	72	1/160	72	1/320	72	1/160	72
Formalin-treated uvea	1/20	48	1/20	65	1/20	48	1/40	48
Choroid	1/80	72	1/320	72	1/160	65	1/320	72
Ciliary body	1/10	48	1/40	48	1/20	48	1/10	48
Iris	1/10	65	1/10	48	1/10	48	0	—

7 illustrates those data and, above all, the striking similarity between the response of the inoculated and control eye.

The next two parts of the studies were concerned with the relationship between the concentration of antigen and the antibody response. To eliminate some irrelevant factors the anterior chamber route was used for inoculation. Table 9 summarizes the results of intracameral injections of concentrated antigen to 200 million organisms per cc. The overall results are the same but the length of antibody production in the inoculated as well as in the control eye was shorter than in the previous experiments (fig. 8).

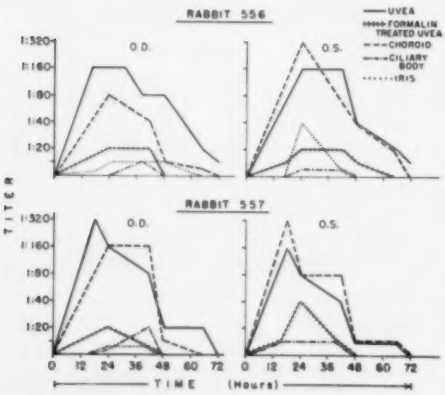


Fig. 7 (Wolkowicz, et al.). Uveal antibody activity in tissue cultures following two injections of typhoid-H (100 million per cc.) in the anterior chamber.

Intracameral injections of 300 million organisms per cc. produced only higher peaks (titer of 1/1280 in control eye of rabbit 561) but had no influence on the span of antibody activity. Here again, as in all the following experiments, a similarity was noted between the inoculated and the control eye (table 10 and fig. 9).

The intravitreal injections of the standard concentration of typhoid-H (100 million organisms per cc.) was somewhat less spectacular than the intracameral injection. In the case of Rabbit 576 (table 11) only the total uvea and choroid participated in antibody formation and the graph (fig. 10) underscores the slightly higher titers in the control eye.

Subretinal injections with the standard vaccine concentration showed a somewhat broader participation of the uveal components (table 12). Here again the graph shows the more intense reaction of the control eye (Fig. 11).

Rabbits subjected to one intraocular antigen injection showed an antibody response which was far from uniform and the ensuing results should be, therefore, critically interpreted. An example in point is Rabbit 563 (table 13 and fig. 12). The first culture media was negative for antibodies and a control media, where no antigen was added to the culture, was negative throughout the experiment. But the addition of antigen to

TABLE 9

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO INJECTIONS OF TYPHOID-H (200 MILLION PER CC.) IN THE ANTERIOR CHAMBER

Material	Rabbit 558				Rabbit 560			
	O.D.		O.S.		O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/160	—	1/160	—	1/40	—	1/40	—
Aqueous	1/20	—	0	—	0	—	0	—
Total uvea	1/80	48	1/160	41	1/10	41	1/80	89
Formalin-treated uvea	1/80	41	1/80	41	1/20	48	1/40	48
Choroid	1/160	48	1/160	48	1/160	48	1/160	48
Ciliary body	1/10	24	0	—	1/10	24	1/10	24
Iris	1/10	24	0	—	0	—	0	—

a culture of the right as well as of the left eye (including the formalin treated uvea) produced a considerable outpouring of antibodies. On the other hand in Rabbits 570 and 571 the cultures not subjected to a second in vitro antigen addition showed almost an identical antibody response. The exception was the left eye in Rabbit 570 where the titer peaks were substantially lower than its, in vitro treated, counterpart. (table 14 and fig. 13).

COMMENT AND CONCLUSIONS

This preliminary work permits us to draw some interesting conclusions which can well be the starting point for further research.

There is no doubt that uveal tissue is capable of yielding antibodies, long after its blood supply is cut off. The uveal response to antigenic stimulus was variable depending on several factors some of which are not yet clearly understood. Those individual differences between rabbit eyes can easily

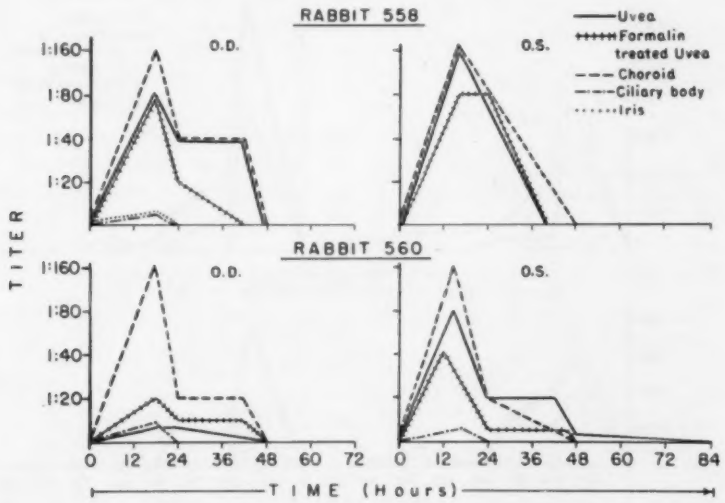


Fig. 8 (Wolkowicz, et al.). Uveal antibody activity in tissue culture following two injections of typhoid-H (200 million per cc.) in the anterior chamber.

TABLE 10

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO INJECTIONS OF TYPHOID-H (300 MILLION PER CC.) IN THE ANTERIOR CHAMBER

Material	Rabbit 561				Rabbit 562			
	O.D.		O.S.		O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/160	—	1/160	—	1/160	—	1/160	—
Aqueous	1/40	—	0	—	0	—	0	—
Total uvea	1/80	89	1/1280	67	1/80	89	1/160	89
Formalin-treated uvea	1/160	48	1/160	48	1/40	48	1/20	48
Choroid	1/320	48	1/1280	89	1/160	48	1/160	24
Ciliary body	0	—	0	—	0	—	1/10	24
Iris	0	—	0	—	1/20	48	1/10	24

lead the enthusiastic experimenter to overgeneralized conclusions.

The antibody production appears to be closely related to the site of inoculation. In this study injection into the anterior chamber appears to be more effective than intravitreal or subretinal injection.

The yield of the three main uveal components is far from equal. The choroid appears by far more active than the ciliary body or iris.

The stock typhoid-paratyphoid vaccine proved to be a weak antigen, but the same suspension concentrated five-fold provoked a vigorous and sustained antibody response. Typhoid-H in concentrations of 100 million organisms per cc. proved to be the most effective antigenic stimulus by inducing a broad span of antibody production. Higher concentrations produced greater peaks in antibody titers but of shorter duration.

It is interesting to note that a weak anti-

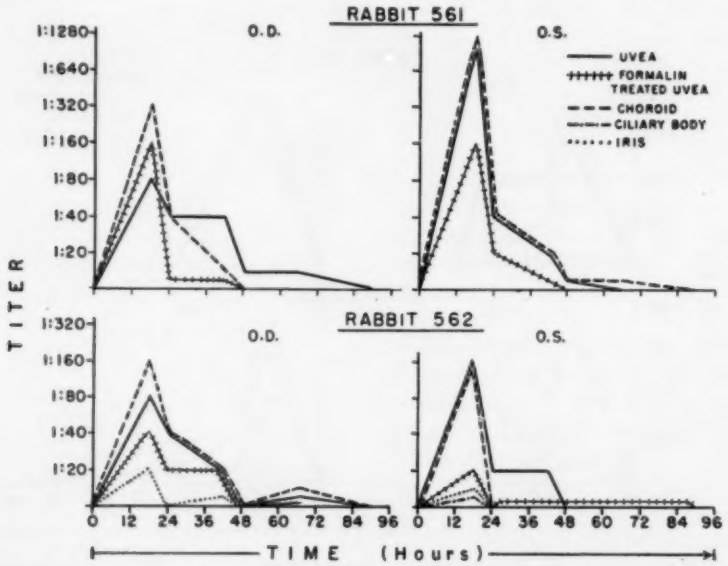


Fig. 9 (Wolkowicz, et al.). Uveal antibody activity in tissue culture following two injections of typhoid-H (300 million per cc.) in the anterior chamber.

TABLE 11

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO INJECTIONS OF TYPHOID-H (100 MILLION PER CC.) IN THE VITREOUS

Material	Rabbit 576			
	O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/20	—	1/20	—
Aqueous	—	—	—	—
Total uvea	1/40	72	1/80	96
Formalin-treated uvea	—	—	—	—
Choroid	1/80	96	1/160	144
Ciliary body	—	—	—	—
Iris	—	—	—	—

gen produced high blood serum titers, low tissue titers and productivity of short duration. The reverse was true with a more potent antigen.

The same can be said of the "sympathetic" response in the control eye. A weak antigen was capable of provoking antibody formation in the inoculated eye only. A concentrated antigen or typhoid-H induced the control eye to produce antibodies at a similar rate as the inoculated eye. Here again the close relationship between low serum titer (or negative serum titer) and vigorous tissue response of the control eye is obvious but its significance is still not clear.

Suspension of the antigen in an emulsion adjuvant did not change appreciably the uveal antibody response. This phase of our

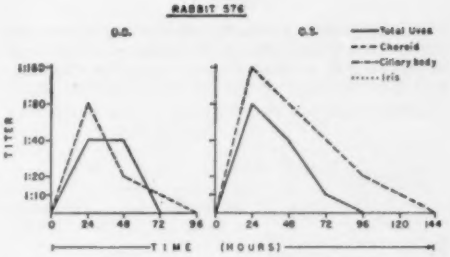


Fig. 10 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following two intravitreal injections of typhoid-H vaccine.

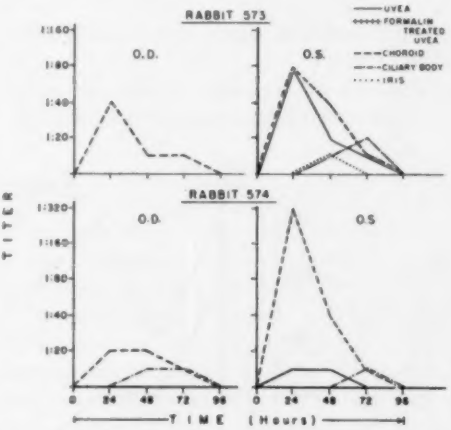


Fig. 11 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity following two typhoid-H vaccine injections in the subretinal space.

TABLE 12

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING TWO TYPHOID-H VACCINE INJECTIONS IN THE SUBRETINAL SPACE

Material	Rabbit 573				Rabbit 574			
	O.D.		O.S.		O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	—	—	—	—	—	—	—	—
Aqueous	—	—	—	—	—	—	—	—
Total uvea	—	—	1/80	96	—	—	1/10	72
Formalin-treated uvea	—	—	—	—	—	—	—	—
Choroid	1/40	96	1/80	96	1/20	96	1/320	96
Ciliary body	—	—	1/20	72	1/10	72	1/10	48
Iris	—	—	1/10	48	—	—	—	—

TABLE 13

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING ONE INJECTION OF TYPHOID-H VACCINE IN THE ANTERIOR CHAMBER AND BOOSTER DOSE ADDED TO THE NUTRIENT FLUID

Material	Rabbit 563			
	O.D.		O.S.	
	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/20	—	1/20	—
Aqueous	—	—	—	—
Total uvea	1/160	264	1/80	144
Formalin-treated uvea	1/20	120	1/80	192
Choroid	1/320	264	1/160	264
Ciliary body	1/20	96	1/20	48
Iris	1/20	240	1/10	48

studies, however, needs considerable additional work.

Presence of antibodies in the culture of formalin-treated uvea suggests an initial reserve of antibodies in the uveal tissue, which could be either produced locally prior to enucleation or deposited through the blood stream. Here a few words of caution are in order. Experience taught us that in order to suppress effectively antibody producing cells it is not enough to immerse the entire globe in formalin. The uvea must be separated from the adjacent tissues and left in formalin for at least two hours. That a few antibody producing cells are capable of surviving this treatment remains a distinct possibility.

Our experiments seem to confirm the statement of Leduc, et al.[10] that antibody formation "requires a latent stimulus and a second stimulus" where the second injection acts as a trigger mechanism. The second antigenic stimulus when added to the nutrient fluid was less effective than when injected

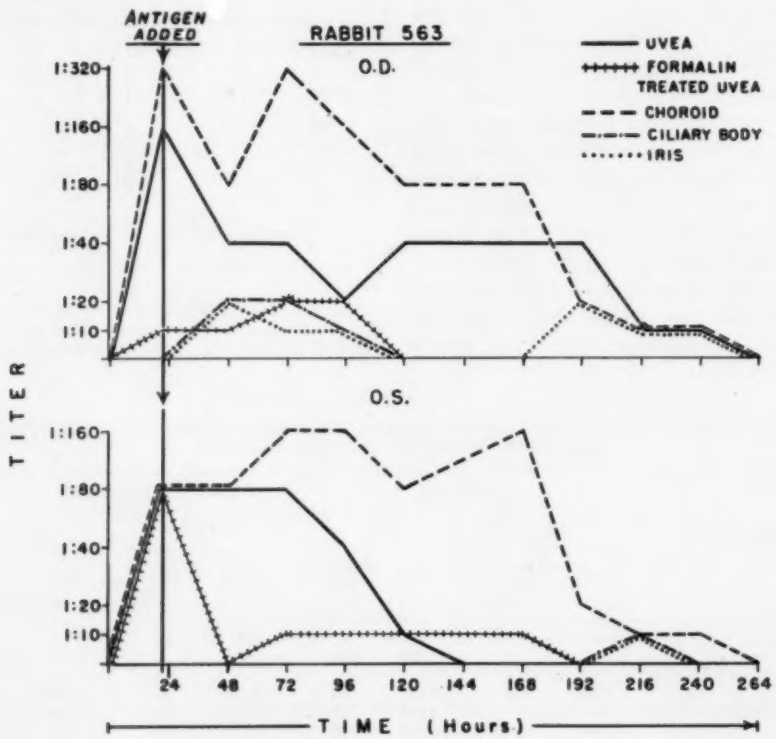


Fig. 12 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following one injection of typhoid-H vaccine in the anterior chamber and booster dose added to the nutrient fluid.

TABLE 14

ANTIBODY TITERS IN BLOOD SERUM, AQUEOUS AND UVEAL TISSUE CULTURES FOLLOWING ONE TYPHOID-H VACCINE INJECTION IN THE ANTERIOR CHAMBER AND BOOSTER DOSE ADDED TO THE NUTRIENT FLUID

Material	Rabbit 570							
	O.D.		O.D.		O.S.		O.S.	
	Control Uvea				Control Uvea			
	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)	Titer	Duration (hr.)
Blood serum	1/20	—	1/20	—	1/20	—	1/20	—
Aqueous	—	—	—	—	—	—	—	—
Total uvea	1/10	96	1/40	120	1/20	120	1/20	120
Formalin-treated uvea	—	—	—	—	—	—	—	—
Choroid	1/10	72	1/40	96	1/80	120	—	—
Ciliary body	1/10	96	1/20	96	1/20	96	—	—
Iris	1/40	72	1/10	72	1/70	72	1/10	72
	Rabbit 571							
Blood serum	1/40	—	1/40	—	1/40	—	1/40	—
Aqueous	—	—	—	—	—	—	—	—
Total uvea	1/20	96	1/40	120	1/20	192	1/20	120
Formalin-treated uvea	—	—	—	—	—	—	—	—
Choroid	1/80	120	1/40	96	1/120	192	1/80	144
Ciliary body	1/10	48	1/10	48	1/40	144	1/20	72
Iris	1/10	72	1/10	48	—	—	1/10	48

in vivo. This was particularly evident when the stock typhoid-paratyphoid vaccine was used as an antigen. In the case of the more effective stimulating typhoid-H vaccine the uveal components started to produce antibodies after a single antigen injection. Moreover, the addition to the culture fluid started, in some instances, a sustained antibody production lasting five or six days.

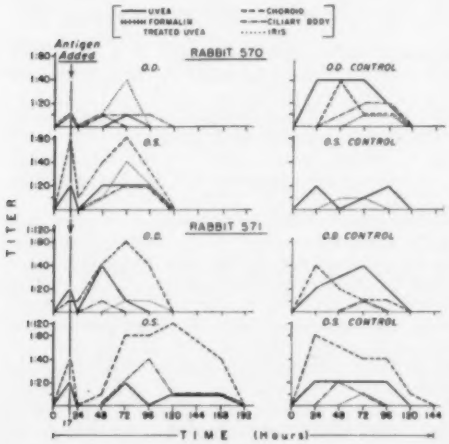


Fig. 13 (Wolkowicz, et al.). Graphic presentation of uveal antibody activity in tissue culture following one injection of typhoid-H vaccine in the anterior chamber and booster dose added to the nutrient fluid. Controls, shown in left half of figure, had no antigen added to culture media.

This work does not include searching and identification of the cell or cells responsible for antibody production in vitro. It is hoped the presently conducted parallel histologic studies, utilizing the Coon's fluorescein conjugation technique, will give us an answer to this problem.

SUMMARY

Literature concerned with antibody formation in tissue culture was briefly reviewed.

Experimental data dealing with intraocular antibody or antibodylike protein formation, were outlined.

The lack of proof of actual antibody production by ocular tissues was emphasized, pointing to the alternative possibilities of excessive seepage of antibodies at the site of antigen accumulation, or migration of exogenous cells having antibody potentials.

Methods of maintaining isolated uveal fragments in nutrient media and the different ways of stimulating antibody response

were described. The accumulated data leave little doubt that uveal tissue is capable of yielding antibodies in vitro.

The intracameral injection of antigen was the most effective for inducement of antibody production.

The choroid gave consistently higher and more sustained antibody titers in vitro from all the uveal components.

A weak antigen (stock typhoid-paratyphoid) vaccine produced a high blood serum titer, low tissue titer and productivity of short duration. Its potency could be enhanced by increasing its concentration to an optimum level.

A more stimulating antigen (typhoid-H) demonstrated the ability to potentiate the uvea to antibody productivity exceeding the blood serum titer. A "sympathetic" response in the control eye was also closely related to antigenic potency and to a low blood serum titer.

There appears to be an optimum of antigenic concentration for a broad span of antibody harvest. Higher concentrations seem to produce greater peaks of shorter duration.

Culture of formalin-treated uvea suggests an initial reserve of antibodies in the uveal tissue, which could be either produced locally prior to enucleation or deposited through the blood stream. One can speculate only that these stored antibodies are the first line of defense to be utilized before the uvea is capable of forming its own agglutinins.

1601 Spring Garden Street(30).

References

1. Witmer, R. H.: The etiological diagnosis of uveitis: I. Arch. f. Ophth., **156**:235-260, 1955.
2. ———: Etiological diagnosis of uveitis: II. Arch. f. Ophth., **156**:337-355, 1955.
3. ———: Etiological diagnosis of uveitis: III. Arch. f. Ophth., **156**:356-373, 1955.
4. ———: Serologie des Kammerwassers-Beitrag zur Atiologie der Uveitis. Monatsbl. f. Augenh., **130**: 234-249, 1957.
5. Thompson, R., and H. Olsen, J.: Antibody production in the rabbit's cornea. J. Immunol., **65**:633-651, 1950.
6. Wolkowicz, M. I., Hallett, J. W., and Leopold, I. H.: Experimental studies on Cx-reactive protein in rabbit aqueous. Arch. Ophth., **59**:389-405, 1958.
7. Fagraeus, A.: Antibody production in relation to the development of plasma cells. Acta Med. Scand., 1948, suppl. 204.
8. Fagraeus, A.: The plasma cellular reaction and its relation to the formation of antibodies in vitro. J. Immunol., **58**:1, 1948.
9. Coons, A. H., Leduc, E. H., and Connolly, J. M.: Studies of antibody production: I. A method for the histochemical demonstration of specific antibody and its application to the study of the hyperimmune rabbit. J. Exper. Med., **102**:49-59 (July-Dec.) 1955.
10. Leduc, E. H., Coons, A. H., and Connolly, J. M.: Studies on antibody production: II. The primary and secondary responses in the popliteal lymph nodes of the rabbit. J. Exper. Med., **102**:61-71 (July-Dec.) 1955.
11. McMaster, P. D.: The nature and significance of the antibody response (A. M. Pappenheimer, Jr., editor.) New York, Columbia Univ. Press, 1953, pp. 13-45.
12. Thorbecke, C. J., and Kenning, F. J.: Antibody formation in vitro by haemopoietic organs after subcutaneous and intravenous immunization. J. Immunol., **70**:129, 1953.
13. Kenning, F. J., and Van der Slikke, L. B.: The role of immature plasma cells, lymphoblasts and lymphocytes in the formation of antibodies, as established in tissue culture experiments. J. Lab. & Clin. Med., **36**:167, 1950.
14. Coons, A. H., and Kaplan, M. H.: Localization of antigen in tissue cells: II. Improvements in a method for the detection of antigen by means of fluorescent antibody. J. Exper. Med., **91**:1-13, 1950.
15. Report from Annual Meeting of the Federation of American Societies for Experimental Biology in Chicago April 15-19, 1957. Med. Sc., May 10, 1957, pp. 27-28.
16. White, R. J., Coons, A. H., and Connolly, J. M.: Studies on antibody production: IV. The role of a wax fraction of mycobacterium tuberculosis in adjuvant emulsions on the production of antibody to egg albumin. J. Exper. Med., **102**:83-103 (July-Dec.) 1955.
17. Foss, B.: Experimental anaphylactic iridocyclitis. Acta path. & microbiol. scandinav., Supp. 81, 1949, p. 1.
18. Vogel, A. W.: Experimental fundal lesions: A method and observations. Arch. Ophth., **51**:535-548 (Apr.) 1954.

PREVALENCE OF OCULAR ANOMALIES AMONG SCHOOL CHILDREN*

A. MAJIMA, M.D.
Nagoya, Japan

A. NAKAJIMA, M.D., AND H. ICHIKAWA, M.D.
Tokyo, Japan

AND

M. WATANABE, M.D.
Shizuoka, Japan

1. INTRODUCTION

Although many reports are found on the statistical aspects of various eye conditions among hospital patients or blind persons, statistics on a general population are less frequent (Ten Doeschate, 1953; Sorsby, et al., 1955; Leverett, 1955; Morgan, et al., 1952). Apparently this is due to the fact that it is much easier to take a sample from the records of hospital patients or blind certificates, but such a sample does not necessarily reflect the true incidence of various eye conditions among an unselected population. Moreover, the absolute incidence of various eye conditions usually cannot be estimated on such figures. A survey of an unselected population is necessary to assess those figures which are important to the public health aspects of ophthalmology, as well as to such hereditary factors as gene frequency of various genetic disorders of the eye.

One of us (Nakajima, 1957) has previously reported a detailed analysis of the prevalence of trachoma based on a survey of an unbiased sample from the population in a rural district of Japan. Some features of trachoma infection important to mass control were described along with an estimation of the social damage caused by trachoma. During the summer vacation in 1958, as part of a consanguinity study, we performed detailed ophthalmic examinations on 3,033 school children in Shizuoka. As primary education is compulsory in Japan, children from primary schools can be regarded as an unbiased, unselected sample of the population of that age group. The school children in a school for the blind in the district were also examined at the same time to make sure that no bias was caused by the blind children having to attend a special school.

Various anomalies of the eye were found among the 3,033 children, giving some basic figures on the prevalence of various ocular anomalies among the population of this age. The result of the survey and the prevalence of various anomalies of the eye found in the survey will be presented here, along with discussion of its implication in social-medical aspects of ophthalmology. The study on the method of screening of color vision defects adopted for this survey was reported in a previous study (Nakajima, et al., 1960).

2. MATERIAL AND METHODS

A detailed description on the material and methods of this survey has already been given in the preceding report (Nakajima, et al., 1960, tables 1 and 2). All children with normal vision (without glasses) were tested with a plus lens for hypermetropia. Those with subnormal vision (without glasses) were first corrected by a minus lens. A detailed re-examination by skiascope and cylindric lenses was carried out on those who failed to obtain normal vision with minus lenses. Careful search was made for the cause of impairment of vision in those who failed to obtain normal visual acuity by correction of the refractive error.

* From the Department of Ophthalmology, Nagoya University, the Department of Ophthalmology, Juntendo University, the Central Hospital, National Railroad Corporation, and the Saiseikai Hospital.

TABLE 1

NUMBER OF CHILDREN EXAMINED DURING THE 1958 SURVEY AT SHIZUOKA

Grade	1	2	3	4	5	Total
M	124	149	410	403	438	1524
F	120	135	400	394	460	1509
TOTAL	244	284	810	797	898	3033

Cover tests alone were adopted for detection of motor anomalies of the eye; the results may be inaccurate in this respect. Tests for visual field and dark adaptation were omitted since most fundus lesions can be picked up by the ophthalmoscope. Some rare conditon, such as changes in the optic pathway, might be missed when it is so slight that no impairment of visual acuity is observed. However, an error of this extent cannot be avoided in a survey such as this, if there is no suitable screening method for testing visual fields or dark adaptation. No slitlamp microscope was used for this survey and minute changes could have been missed; however, such minute changes have only slight significance for the purpose of this survey. The type 2 hand fundus camera of Dr. Noyori was used to record some of the significant changes found in the survey.

3. RESULTS

Various frequent and rare anomalies of the eye were found among the 3,033 children examined. Anomalies in color sense were reported in a previous study (Nakajima, et al., 1960). Other anomalies of the eye are tabulated in Tables 3 and 4; Table 5 gives the result of the examinations of blind school children.

A. COLOR VISION DEFECTS

Eighty-one color vision anomalies were identified by anomaloscopic examination. Variation from normal was usually clear cut but one deuteranomalope, who misread 13 out of 16 plates showed a range close to normal, although outside the normal range. One normal who misread five plates was at the border of normal. There was no distinct relationship between the position or width of the equation range and number of misreadings.

Among 81 color defectives found, 77 (5.05 percent) were male and four (0.26 percent) were female, a figure which coincides with the theoretical distribution of color defects among males and females (5.0 percent)^2 = 0.25 percent).

This agreement is further fulfilled in the distribution of various types of color vision defects: In males, 31 deuteranomalies (Da); 35 deuteranopes (D), seven protanomalies (Pa) and four protanopes (P) were found. These figures account for Da, 2.1 percent; D, 2.2 percent; Pa, 0.46 percent and P, 0.26 percent respectively. Three extreme deuter-

TABLE 2

SYSTEM OF OPHTHALMOLOGIC EXAMINATIONS

1. Visual acuity and refractive error
   3 test types (one for illiterates); natural illumination (500–3,000 lux); 2 assistants, a set of lens plates
2. Color vision
   25 selected plates from the newest (13th) edition of Ishihara test (7 plates are for illiterates); artificia illuminant-C; Plates No. 5 and No. 6 of HRR test, a plate made by Dr. Okayasu; one assistant; anomaloscopic test for suspective color vision defects (two instruments) anomaloscopic examination performed by Dr. Ichikawa, Dr. Majima, and Dr. Nakajima.
3. Routine ophthalmologic examinations (objective) done by Dr. Majima
   Cover test for phoria and tropia; oblique illumination with magnifier; ophthalmoscopic examination; photographic recording of the selected findings by fundus (done by Dr. Baba).

anomalies and one extreme protanomaly were found. As genes for anomalies are dominant over genes for opies, the theoretical requirement for the distribution of Da and D in females is calculated to be Da, 0.14 percent and D, 0.05 percent. Three deuteranomalies and one deuteranope were found among the females and this number is as close as possible to the theoretical requirement. No protan was found among the females. The prevalence of color vision defects in males (5.05 percent) is significantly higher than the standard for Japanese males (4.45 percent), this difference being significant statistically.

B. Refractive errors

Refractive errors, measured without cycloplegia, are tabulated in Table 3. Results are given, for convenience, in terms of number of eyes instead of number of cases. About one percent showed more than one diopter of hyperopia, whereas, more than 10 percent had myopia of more than one diopter. If refractive errors of 0.5 diopter were taken into consideration, these figures are reversed to 29 percent hyperopia and 12 percent myopia, the remaining 59 percent being emmetropic. The mean of the refraction is slightly hyperopic until the fourth grade (aged nine years) and turns myopic at the fifth grade (aged 10 years). The mean of refractive error of more than one diopter for the hyperopic and myopic groups reveals that there is no definite tendency for the hyperopic group, whereas the myopic group increases from the third grade up and the mean of the female group is larger in third, fourth and fifth grades.

A total of 34 eyes were found to have low visual acuity which could not be corrected to normal by lenses. Various pathologic conditions were found as the cause of visual impairment. The results are given in Table 3A. Table 3A shows that none of the four children whose vision was less than 0.02 was binocular. Among the group where vision is between 0.1-0.02, three children

TABLE 3

Distribution of refractive errors

Grade of Refraction	1			2			3			4			5			Total
	m	f	t	m	f	t	m	f	t	m	f	t	m	f	t	
+4.0	0	0	0	0	0	0	2	0	2	0	0	0	0	0	0	2
+3.0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1
+2.0	1	0	1	0	1	1	0	1	1	3	0	3	4	0	4	10
+1.5	1	0	1	1	2	3	5	11	16	0	0	0	0	0	0	20
+1.0	25	70	145	64	68	132	258	222	480	245	275	520	254	247	501	1778
+0.5	143	133	276	194	164	358	444	411	855	466	452	918	512	528	1040	3447
−0.5	16	26	42	27	27	54	62	89	151	37	32	69	31	47	78	394
−1.0	6	8	14	7	6	13	32	25	57	19	7	26	20	34	54	164
−2.0	3	3	6	5	3	8	9	16	25	16	9	25	18	26	44	110
−3.0	1	0	1	0	0	0	4	10	14	8	3	11	5	11	16	42
−4.0	2	0	2	0	0	0	2	4	6	5	5	10	6	9	15	33
−5.0	0	0	0	0	0	0	1	2	3	1	0	1	1	2	3	7
−6.0	0	0	0	0	0	0	0	2	2	0	1	1	2	3	5	8
−7.0	0	0	0	0	0	0	0	0	0	0	0	0	2	5	7	7
−8.0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	3	3
−9.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	248	242	490	298	271	569	819	793	1613	800	785	1585	856	915	1771	6027
Mean Refraction	+0.05	+0.02	+0.03	+0.02	+0.04	+0.035	+0.05	+0.04	+0.00	+0.01	+0.06	+0.04	+0.00	+0.14	+0.07	+0.00
Mean of Hyperopia (≧−1D)	+1.5	—	+1.5	+1.0	+1.25	+1.2	+2.0	+1.0	+1.6	+2.0	—	+2.0	+2.0	+3.0	+2.2	+1.5
																331
Mean of Myopia (≦−1D)	−1.79	−1.31	−1.54	−1.25	−1.22	−1.24	−1.34	−1.26	−1.78	−1.85	−2.86	−2.20	−2.27	−2.53	−2.46	−2.0
																(372)

TABLE 3A

OTHER CONDITIONS FOUND AS CAUSES OF VISUAL IMPAIRMENT

Condition	Male	Female	Total	0.5–0.2	0.1–0.02	Less than 0.02
Aphakia						
(congenital cataract)	4	2	6	0	6 (3)*	0
(trauma)	1	1	2	0	0	2 (2)
Phthisis bulbi						
(trauma)	1	0	1	0	0	1 (1)
Corneal opacity	4	1	5	2 (1)	3 (3)	0
Nystagmus	4	4	8	6 (3)	2 (1)	0
Microphthalmos	2	0	2	0	2 (1)	0
Amblyopia						
(fundus atrophy)	1	0	1	2 (1)	0	0
(anisometropia and hyperopia)	2	1	3	3 (3)	0	0
(motor anomaly)	0	2	2	0	2 (2)	0
(conus inf.)	2	0	2	2 (1)	0	0
(strong astigmation)	0	1	1	1 (1)	0	0
Persistent pupil membrane	1	0	1	0	0	1 (1)
TOTAL	22	12	34	16 (10)	15 (10)	4 (4)
NOT RECORDED	5	0	5			
TOTAL REFRACTED	3021	3006	6027			
SUM TOTAL	3048	3018	6066			

* Figures in parentheses indicate number of children.

with aphakia after congenital cataract, one with nystagmus and one with microphthalmos had impaired binocular vision. Six cases in the 0.5-0.2 vision group were also binocularly impaired. This result suggests that cataract, nystagmus, and microphthalmos are prevalent among the various congenital anomalies which lead to visual impairment, and that corneal opacity and trauma are important postnatal changes leading to loss of visual acuity.

C. MOTOR ANOMALIES

The results on motor anomalies are tabulated in Table 4 which is the only table in which the number of cases are listed instead of the number of eyes. It is rather unexpected that exophoria was predominant over esophoria. This might have been due partly to error in technique although our clinical experience suggests that the cover test is reliable. This tendency should be accepted until more detailed studies are available. There may be some relationship between this finding and the fact that hyperopia found was of slight grade (0.5 diopter). The number of cases of exotropia and esotropia were, however, comparable in number, each about 0.3 percent. Only one out of seven children with esotropia was found to be amblyopic in one eye. No amblyopia was found among those with exotropia. Likewise, four out of eight cases of nystagmus showed impairment of vision.

D. ANOMALIES OF THE FUNDUS

A temporal crescent was found in 74 (1.2 percent) of the eyes, an inferior one in 53 (0.87 percent) and a nasal one in six (0.1 percent). Physiologic excavation of the disc was found in 206 (three percent) eyes. A tessellated fundus and vasa cilioretinalis were found in a comparable number of eyes. Among rarer changes were medullated nerve fibers, four cases (0.06 percent), chorioretinal atrophy around the disc, origin unknown, two cases (0.03 percent); coloboma of uvea, two cases; and an eye each of persistent hyaloid artery, coloboma of the disc, and an unidentified anomaly of the disc. It is interesting that most anomalies of or around the disc were found in females. It is not unexpected that such abiotrophic changes of the fundus as retinitis pigmentosa were not found, since the school children examined

were too young for these conditions to be manifest.

E. Anomalies of the lens

Cataracts of various origin were found in 21 (0.34 percent) eyes. Among them six cases had already been operated, with poor visual acuity at present. These cases were all considered to be of congenital origin; and in two of them the fathers suffered from the same condition. Two eyes out of three with traumatic cataract were nearly blind, and only one case preserved fairly good vision (0.7). Hardly any visual impairment was observed in 12 eyes with congenital cataract. An eye with probable retrolental fibroplasia was found.

F. Anomalies of other parts of eye

Anomalies of the iris, cornea, sclera, conjunctiva, and eyelids are tabulated in the lower part of Table 4. One case among 31 of persistent pupillary membrane was so severe that visual acuity was greatly impaired. Corneal opacities were found in 23 eyes but the visual acuity was severely impaired in only five of them. Other anomalies found were mostly anomalies of pigmentation in various parts of the eye. A few cases of partial decoloration of the iris were found and classified as heterochromia of the iris.

G. Comment

The results of this survey give some idea of the prevalence of various anomalies of the eye in an unselected population of the age of six to 10 years. Among various ocular changes, those causing visual impairment have direct clinical and practical importance. Visual impairment can often be improved by glasses. Table 3 reveals that, although refraction tends toward hyperopia, the grade of hyperopia, measured without cycloplegia, is only about 0.5 diopter. Although there were 33 eyes with hyperopia of more than one diopter, three could not be corrected to normal, probably due to accompanying anisometropia and amblyopia. There were more than 10 times as many myopic eyes of more than one diopter as hyperopic but not one was amblyopic. It is interesting that the prevalence of myopia and mean of myopia are larger in females than in males. Investigation of general body growth also shows the same tendency, which suggests the importance of the growth process in the incidence of myopia.

The findings in 24 children with impaired vision in one or both eyes show that not one is blind in the strict sense. Since it is doubtful whether those with less than 0.4 binocular vision can follow a normal educational course, the need for some special class for them is suggested. Twelve cases with binocular vision of less than 0.5 account for 0.4 percent of those who were examined.

Among 34 eyes with impaired vision, the pathologic condition in only seven is considered to be of environmental or postnatal origin; in all of the remaining 27 eyes the condition was either congenital or hereditary. This was also noted during detailed clinical examinations of 121 children in the Shizouka Blind School (table 5). Among 121 children, 84 (73 percent) were found to have lesions of congenital or hereditary origin and, in this group, the rate of consanguinity was found to be 22.6 percent compared with eight percent in the other group. More detailed studies are being made regarding this. It is also interesting to note that the rate of consanguinity is very high in chorioretinal atrophy. No consanguinity was found in optic atrophy and strong myopia; however, the number of cases for each group was small.

A few remarks should be made on the results given in Table 4. It is a rather unexpected finding that exophoria is predominant over esophoria even in these age groups. This may be related to the finding that most of the hyperopias were of slight degree; hyperopia of more than one diopter is not found so frequently without cycloplegic examination, which suggests that a slightly abduced position is structurally stable.

TABLE 4

PREVALENCE OF VARIOUS ANOMALIES OF THE EYE IN SURVEY OF 3,033 SCHOOL CHILDREN

		Grade					
		1	2	3	4	5	Total
1. MOTOR ANOMALIES							
Exophoria	M	19	19	38	39	39	154
	F	12	17	39	36	39	1
	Total	31 (12.7)	36 (12.6)	77 (9.5)	75 (9.4)	78 (8.7)	297
Esophoria	M	0	0	0	1	1	2
	F	0	0	4	0	3	7
	Total	0	0	4	1	4	9
Exotropia	M	0	0	0	1	2	3
	F	0	0	1	4	2	7
	Total	0	0	1	5	4	10
Esotropia	M	1	0	0	1	0	2
	F	0	1	1	1	2	5
	Total	1	1	1	2	2	7
Nystagmus	M	1	2	0	1	1	5
	F	0	0	0	0	3	
	Total	1	2	0	1	4	8
Paralysis of muscle & ptosis	M	0	0	0	1	0	1
	F	0	0	2	0	0	2
	Total	0	0	2	1	0	3
2. ANOMALIES OF FUNDUS (number of eyes found)							
Crescent (conus)							
Temporal	M	0	2	19	18	5	44
	F	0	1	8	12	9	30
	Total	0	3	27	30	14	74
Inferior	M	2	1	6	7	4	20
	F	5	1	10	2	15	33
	Total	7	2	16	9	19	53
Nasal	M	0	0	2	0	0	2
	F	0	0	4	0	0	4
	Total	0	0	6	0	0	6
Physiologic excav. disc	M	6	2	45	34	28	115
	F	4	4	26	30	27	91
	Total	10	6	71	64	55	206
Fundus tessel.	M	6	14	24	30	34	108
	F	4	2	12	22	46	86
	Total	10	16	36	52	90	194
Vasa cilioret.	M	5	8	15	18	17	63
	F	2	10	16	17	32	77
	Total	7	18	31	35	49	140

Rarer anomalies of the fundus
Medullated nerve fiber—M. 0, F. 4
Coloboma of the disc—F. 1
Unidentified anomaly of the disc—F. 1
Chorioretinal atrophy around disc—M. 2
Coloboma of uvea with microphthalmos, nystagmus—M. 2
Persistent hyaloid artery—M. 1
Total—11 eyes

TABLE 4 (*Continued*)

		Grades					
		1	2	3	4	5	Total
3. ANOMALIES OF LENS							
Congenital cat.	M	0	0	5	1	2	8
	F	0	0	1	1	2	4
	Total	0	0	6	2	4	12
Traumatic cataract	M	0	0	0	1	0	1
	F	0	0	1	1	0	2
	Total	0	0	1	2	0	3
Aphakia and after cat.	M	0	2	2	0	0	4
	F	0	0	0	0	2	2
	Total	0	2	2	0	2	6
TOTAL		0	2	0	4	6	21
Rarer anomalies							
Retrolental fibroplasia (?)—F. 1							
4. ANOMALIES OF IRIS							
Persistent pupil membrane	M	4	1	3	3	3	14
	F	3	3	2	7	2	17
	Total	7	4	5	10	5	31
Heterochromia iridis	M	1	26	34	30	48	139
	F	4	14	15	47	52	132
	Total	5	40	49	77	100	271
Melanosis iridis	M	6	5	5	3	8	27
	F	3	4	9	11	2	29
	Total	9	9	14	14	10	56
5. ANOMALIES OF CORNEA, SCLERA, CONJUNCTIVA AND EYELIDS							
Corneal opacity (inc. regular astigmatism)	M	2	2	3	1	3	11
	F	0	2	4	3	3	12
	Total	2	4	7	4	6	23
Entropion and trichiasis	M	4	8	13	5	8	38
	F	3	7	5	14	6	35
	Total	7	15	18	19	14	73
Epicanthus	M	22	27	88	84	128	349
	F	14	26	72	94	110	316
	Total	36	53	160	178	238	665
Melanosis palpebrae	M	0	0	1	1	5	7
	F	0	1	4	0	3	8
	Total	0	1	5	1	8	15
Conjunctiva & sclera	M	1	5	7	5	2	20
	F	4	2	6	2	4	18
	Total	5	7	13		6	38

SUMMARY

A detailed ophthalmic examination was performed on 3,033 school children, aged from six to 10 years. The prevalence of various anomalies of the eye in an unbiased population was obtained. The relation of the incidence of myopia to growth and sex was noted. The importance of congenital anomalies of the eye as a cause of visual impairment was stressed. Special reference was made to children in the school for the blind where the rate of consanguinity was high in those with congenital eye defects. The preva-

TABLE 5

CAUSES OF BLINDNESS AT SHIZUOKA BLIND SCHOOL (1958–9)

	No. Cases		
	Male	Female	Total
Congenital			
Congenital cataract	16 (2)	6 (2)*	22 (4)
Microphthalmos	12 (2)	9 (0)	21 (2)
Atrophia retinochor.	6 (3)	3 (3)	9 (6)
Buphthalmos.	5 (2)	2 (1)	7 (3)
Atrophia n. optici	2 (0)	4 (0)	6 (0)
Strong myopia.	3 (0)	4 (0)	7 (0)
Nystagmus with amblyopia.	4 (1)	2 (0)	6 (0)
Amotio falcif. congenita.	1 (1)	1 (1)	2 (2)
Albino	1 (0)	1 (1)	2 (1)
Other condn. (retrol. fibropl., amotio probably congenital)	2 (0)	0	2 (0)
Total	52 (11)	32 (8)	84 (19) (22.6%) (70%
Postnatal.			
Trauma	6 (0)	3 (0)	9 (0)
Inflammations	8 (1)	6 (2)	14 (3)
Keratomalacia	6 (0)	6 (0)	12 (0)
Amotio ret.	2 (0)	0	2 (0)
Total	22 (1)	15 (2)	37 (3) (8%) (30%)

* Figures in parentheses indicate number of children of consanguineous origin.

lence of motor anomalies suggested need for an orthoptic school.

ACKNOWLEDGMENT

We acknowledge with gratitude the support of the Consanguinity Study Team headed by Prof. T. Komai. We wish also to express our appreciation for the warm support and useful suggestions of Prof. T. Komai and Prof. K. Kojima of Nagoya University and Prof. T. Sato of Juntendo University.

REFERENCES

Leverett, H. M.: Am. J. Ophth., **39**:I 527-40, 1955.
Morgan, A. L., Crawford, J. S., Pashby T. J., and Gaby, J. R.: Canad. M. A. J., **67**:29-34, 1952.
Nakajima, A., Majima, A., Ichikawa, H., and Watanabe, M.: in press.
Nakajima, A., and Otake, T.: Rev. Intern. Trach. **4**:398-438, 1957.
Sorsby, A., Benjamin, B., and Yudkin, J.: Brit. J. Soc. Prev. Med., **9**:1-9, 1955.
Ten Doeschate, G.: Aeromed. Acta, **2**:141-155, 1953.

OPHTHALMIC MINIATURE

Down, England, Mar. 18, 1871

To Professor F. C. Donders:

I have been interested about your views published in 1848. It is clear to me that you were as near as possible in preceding me on the subject of Natural Selection.

Charles Darwin.

NOTES, CASES, INSTRUMENTS

PRIMARY LYMPHOSARCOMA OF THE CONJUNCTIVA*

SIDNEY LERMAN, M.D.
Rochester, New York

Secondary involvement of the eye and orbit occurs in about two to four percent of patients with generalized lymphosarcomatosis and/or other forms of lymphomatous tumors.[1-3] Of the extranodal primary lesions which are a more rare manifestation of lymphosarcoma, only one percent occur in the eye and orbit.[1,4] Primary lymphosarcoma of the conjunctiva is consequently a relatively uncommon condition. The purpose of this paper is to report two such cases in which there was no evidence of lymphosarcoma elsewhere in the body.

CASE REPORTS

Both patients† (a white man, aged 51 years, a white woman, aged 42 years) presented with complaints of a painless elevated discoloration in the left eye of relatively recent onset. They were both in apparent good health and a subsequent complete examination failed to reveal any other evidence of lymphosarcoma.

Clinically, lymphosarcoma of the conjunctiva presents a unique characteristic picture. It consists of an elevated tumor mass (fig. 1) which has a salmon-pink color. The overlying conjunctiva is smooth and the borders of the lesion are quite well demarcated. The diagnosis in both cases was confirmed by biopsy.

Microscopic examination of the biopsy specimen from the first case (the man) revealed a heavy infiltration of small dark-staining cells in the subconjunctival tissue (fig. 2), compatible with a diagnosis of lymphocytic cell lymphosarcoma.

Microscopic examination of the biopsy material obtained from the second case (the woman) showed dense cords of small, dark round cells almost completely replacing the subconjunctival tissue (fig. 3). A higher magnification of this lesion (fig. 4) revealed the lymphocytic nature of this lymphosarcoma.

Both cases were treated by local radiation therapy and the lesions regressed rapidly and completely disappeared. There has been no sign of recurrence, either at the primary site or elsewhere, several months after completion of the radiotherapy.

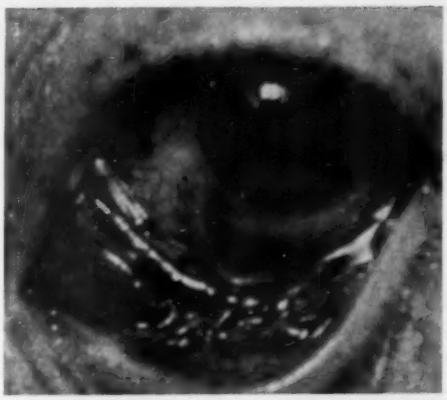


Fig. 1 (Lerman). Primary lymphosarcoma of the lower palpebral conjunctiva (a man, aged 51 years).

COMMENT

The prognosis of lymphosarcoma (five-year survival rate) depends on whether the patient is suffering from the localized or generalized form of the disease. Catlin[5]

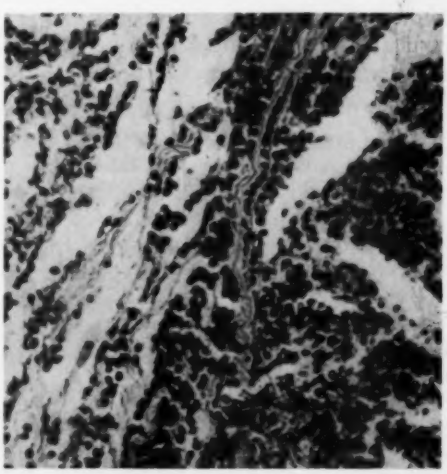


Fig. 2 (Lerman). Biopsy section of lesion shown in Figure 1 (×378).

* From the Department of Surgery, Division of Ophthalmology of the University of Rochester School of Medicine and Dentistry. This study was supported by funds granted by the Rochester Eye Bank and Research Society.

† Drs. J. R. Fitzgerald and S. J. Ianacone granted permission to report these cases.

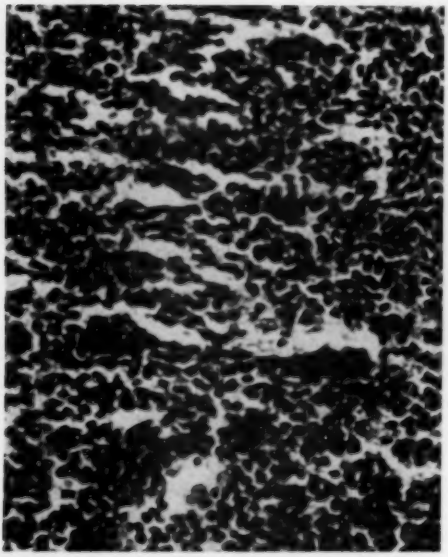


Fig. 3 (Lerman). Biopsy section of primary lymphosarcoma of the conjunctiva from the second case (a woman, aged 42 years). (×378.)

stressed the relatively favorable prognosis in lymphosarcoma of the head and neck region in contrast to the generalized form; he reported a 60-percent five-year- survival rate in patients who had a primary lesion at the time of the original diagnosis. Radiotherapy is the preferred form of treatment, and the results are significantly better in the localized form of the disease.[6]

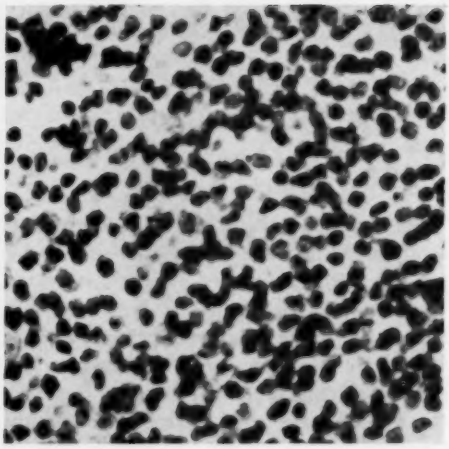


Fig. 4 (Lerman). Higher magnification of Figure 3, showing lymphocytic nature of the lesion (×658).

The prognosis in those cases in which the primary lesion of lymphosarcoma first becomes manifest in the eye is probably even more favorable than for primary lymphosarcoma elsewhere, since the patient will usually become aware of the lesion at an earlier date and consequently the diagnosis is made and therapy instituted at an earlier date. These observations are especially applicable to the two patients reported here in which the lesion first became manifest in the conjunctiva and the disease was apparently localized to this region.

260 Crittenden Boulevard (20).

References

1. Sugarbaker, E. D., and Craver, L.F.: J.A.M.A., **115**:17; 112, 1940.
2. Heath, P.: Am. J. Ophth., **32**:1213, 1949.
3. McGavic, J. S.: A.M.A. Arch. Ophth., **53**:236, 1955.
4. Friedenwald, J. S.: An Atlas and Textbook of Ophthalmic Pathology. Philadelphia, Saunders, 1952, p. 197.
5. Catlin, D.: Am. J. Roentgenol., **59**:354, 1948.
6. Stout, A.P., J.A.M.A., **118**:968, 1942.

MANIPULATION OF CONTACT GLASS*

John Thayer Simonton, M.D.
Rye, New York

The value of the contact glass to study the anterior chamber and the fundus has been established. However, it is my feeling that it would be used more frequently in routine office practice if a relatively fast, simple technique were developed to make the procedure less alarming for the patient and easier for the doctor.

It has been my observation that most

* From the Department of Ophthalmology, New York Eye and Ear Infirmary.

Fig. 1 (Simonton). Technique of inserting contact glass. (See text for details.)

ophthalmologists use two hands to insert the contact glass. I have found this method quite awkward, especially with the newer types of slitlamps where the position of the optical system makes it difficult to use both hands to insert the contact glass.

For the past 18 months I have been using the one-handed technique to insert the contact glass and have found it to be satisfactory.

Method

First a topical anesthetic, such as pontocaine (0.5 percent) is instilled into the conjunctival sac. A drop of 0.5-percent methyl cellulose solution is placed in the concavity of the contact glass, being careful to avoid air bubbles.

The patient is asked to look straight ahead. However, if there is a large overhanging brow, it is easier to have them look down about 10 degrees.

The ring finger is used to pull down the lower lid (fig. 1-a). The middle finger elevates the upper lid (fig. 1-b). Then by turning the wrist toward the eye, the contact glass is placed on the cornea (fig. 1-c).

The contact glass may then be rotated to the desired position by gently pressing the contact glass against the globe with the index finger, while the thumb and third finger turn the contact glass to the desired position (fig. 1-d).

To remove the contact glass, the patient is asked to look down and the contact glass is lifted off the eye.

The three-mirror contact glass, which is considerably larger than the contact glass demonstrated, is just about as easy to handle.

With a little practice, dexterity in handling the contact glass with either hand is rapidly developed.

Summary

A new one-handed method of handling the single or multiple mirrored contact glass is presented.

The advantages of this method are:

1. Faster and easier manipulation
2. One hand is free to operate the slitlamp.

66 Milton Road.

A UNIVERSAL PHOTOSTIMULATOR*

J. François, M.D., and G. Verriest, M.D.
Ghent, Belgium

For several years we have attempted to build an apparatus which could furnish light stimulation of which the chief characteristics—rigidly controlled—could be independently varied (wavelength, luminance, and apparent object size, exposure time or flicker frequency of the object, its localization in the visual field, luminance of the background on which the object is presented and so forth). We also wanted an extensive range of luminance available so that the apparatus could be suitable not only for subjective determination of perception thresholds but also for the study of the electroretinogram.

The design of an apparatus of these qualifications met with very considerable difficulties, in view of the precision aimed at. Direct collaboration between Mr. R. Dudragne

* From the Ophthalmological Clinic of the University of Ghent (Prof. J. François).

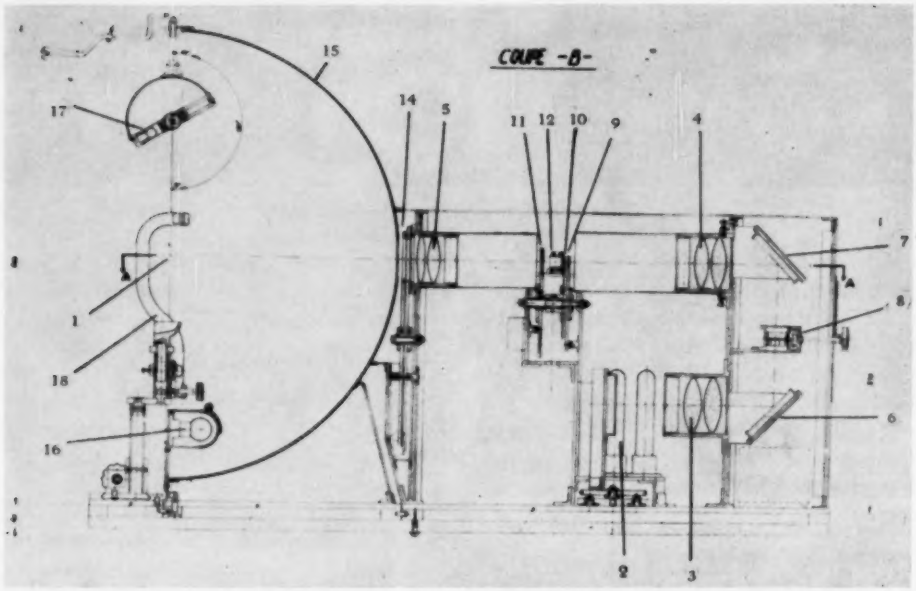


Fig. 1 (François and Verriest). Universal photostimulator. (1) Pupillary field of the examined eye. (2) Light sources. (3, 4, 5) Objectives. (6, 7) Plane mirrors. (8) Photometric wedge. (9) Diaphragms conjugated with the pupil of entry of the eye examined. (10) Rotating disc. (11) Color filters. (12) Semireflective mirror. (13) Telescope. (14) Plage diaphragms. (15) Dome. (16) Lamp for the eventual illumination of the dome. (17) Projector. (18) Headrest.

and ourselves has made it possible, after repeated efforts over a period of three years, to present an apparatus capable of coping with the problems of controlled photostimulation.

With a view to obtaining various different wavelengths we resorted to the use of spectral lamps fed by continuous current.

In the course of our investigations it also became apparent that, in order to obtain the high luminances which we desired, it was necessary to develop an optical system furnishing a light beam concentrated on the pupil of the eye under examination. This solution, moreover, had two other important advantages:

1. With the aid of additional devices it is possible to vary the diameter of the effective pupil of entry, to determine its dimension and its localization in the anatomic pupil in such a way that the apparatus can also be used to study directional effects.

2. The concentration of light on a small surface makes it easy to use the apparatus for experiments with animal eyes.

The apparatus has meanwhile been finished (figs. 1 and 2).

I. A *set of lenses* makes it possible to throw onto the pupillary field of the eye (1) such light as is produced by the light sources (2) and modified by the various devices to be described.

The large number of these devices made it necessary to use two intermediary image foci, in the planes of which are placed filters, diaphragms and flicker system. The objectives (3, 4, 5) are of large diameter and large relative aperture; they meet the requirements of Clairault-Mossotti. The light bundle is reflected twice by plane mirrors in order to reduce the length of the photostimulator. This optical system ensures exact con-

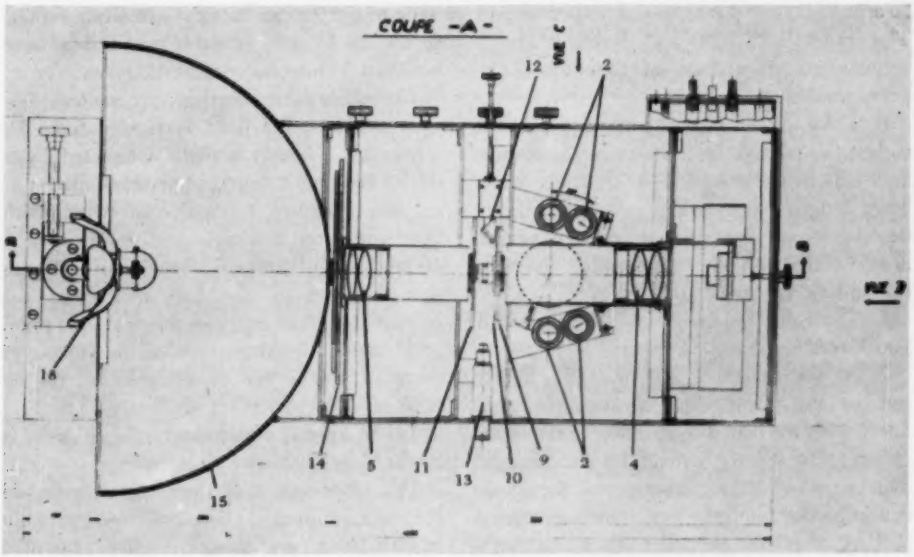


Fig. 2 (François and Verriest). Universal photostimulator. (See legend of Figure 1.)

jugation of the light sources, the various diaphragms and the pupil of the eye examined.

II. The *electrical schema* was devised in such a way that all parts of the photostimulator are fed with continuous current. The current from the supply circuit is stabilized and transformed into continuous current (for feeding the lamps on the one hand, and the flicker system on the other) in a box completely isolated and separated from the photostimulator: the latter therefore receives only continuous current, and care has been taken to avoid any risk of a residual alternating current, regardless of its origin, which might produce artefacts. The eye examined, the surrounding dome and the remainder of the photostimulator are each isolated from the other.

III. Apart from the lenses and the mirrors, the mechanical devices and the electrical installation, the photostimulator consists of the following principal parts:

1. An *incandescent lamp,* providing white light of color temperature equivalent to 3.000°K. and, on the other hand, mercury, cadmium and argon lamps. All these lamps (*2*) are supplied with continuous current by a dry rectifier. They are separately used, with the aid of mirror devices.

2. A *mechanical shutter,* ensuring exposure times between 0.04 and 0.004 sec, makes it possible to produce flashes apart from those produced by the flicker apparatus described below. The shutter is also fitted with a two-stage exposer.

3. A photometrically neutral *wedge* (8) makes it possible to obtain continuous variations in luminance on a logarithmic scale of 10 decimal units.

4. *Diaphragms* (9), varying in aperture diameter from 3.91 to 0.56 mm. are conjugated with the pupil of entry of the eye examined and placed exactly at the level of one of the two image foci of the optic system. They make it possible to vary the diameter of the pupil of entry from 7.0 to 1.0 mm.

5. A *rotating disc* (10), operated by a motor fed by continuous current, makes it possible to obtain intermittent stimulations to

be adjusted from 1.0 to 80 phases per second. The intervals of light and darkness are always equal, regardless of the flicker frequency selected.

6. *Color filters* (11) make it possible to isolate the rays from the mercury, cadmium and argon lamps, and to separate wider wave length bands when using the incandescent lamp. Ten color filters are permanently fitted on the apparatus: maximal transmissions are found at 404.7, 435.7, 467.8, 508.6, 546.1, 574.0, 643.8, 696.5, 706.7 and 750.4 mμ.

7. A semireflective *mirror* (12), which can be put away, and a *telescope* (13) fitted with an ocular micrometer enable the observer to see the eye under examination and to measure the diameter and the localization of the spotlight in the anatomic pupil.

8. A *photoelectric cell* enables the registration of changes in light stimulation on one of the leads of the electroretinograph.

9. A detachable *frosted glass* makes it possible to transform stimulation by directed light into stimulation by nondirected light.

10. *Diaphragms* (14) with aperture diameters stepped up between 1.1 mm. and 67 mm., according to a logarithmic scale for the surfaces, make it possible to vary the apparent diameter of the area from 10 minutes to 10 degrees. The diaphragm surfaces (on the side of the eye examined) are painted dull white.

11. The surrounding *dome* (15) is hemispherical and has a radius of 375 mm. It is painted dull white and can be illuminated by a lamp (16) supplied with continuous current; the luminance in the dome agrees with Lambert's law and may be modified by moving a screen in front of the lamp. This screen is shaped so that its displacement on a linear scale more or less corresponds with a logarithmic variation in the dome luminance.

12. A white or red point of fixation may be projected onto the dome with the aid of a *projector* (17) fitted in the upper part. This projector can be aimed in all directions according to two gradated quadrants (one horizontal and one vertical).

13. When determinations are made in human subjects, the head is rigidly fixed by means of a *headrest* (18) completed by a device bearing a dental imprint. A mechanical device makes it possible to switch with precision from the right to the left eye. A sliding gauge shows 0.10-mm shift, during determination of the displacement of the effective pupil of entry in the anatomic pupil and during determination of the displacement of the center of eye-rotation in the field of observation.

14. In animal experiments the chinrest is replaced by a *plank* with grooves.

IV. *Illumination* of the pupil of entry of the eye examined has been *calibrated* not only in CIE units (gradation B 4880°K) but also in energetical units. This gradation has been effected both for white light and for the various colored lights, as well as for different positions of the photometric wedge. The luminances of the outlet lens and the retinal illumination in trolands can be calculated. The luminances of the surrounding dome are also calibrated.

This photostimulator makes it possible to study a large number of psychophysical data in man, and also permits further investigation of electroretinography in man and in animals.

Summary

The universal photostimulator makes it possible to vary at will numerous modalities of observation of a test object: spectral composition, luminance, apparent diameter, exposure time for an isolated stimulus or frequency for intermittent stimulation, localization in the visual field, diameter of the effective pupil of entry, localization of the effective pupil of entry in the anatomic pupil, and luminance of the environment.

The apparatus operates on continuous current and is calibrated in CIE units and energetical units. It affords unlimited possi-

bilities not only from a clinical point of view but especially in terms of investigation of sensory physiology, both for subjective determinations and for electroretinographic studies.

Akademisch Ziekenhuis
De Pintelaan

BILATERAL LENS OPACITIES*

Associated with use of di-isopropyl fluorophosphate eyedrops

Raymond Harrison, M.B.
Boston, Massachusetts

The use of di-isopropyl fluorophosphate (DFP) in the treatment of accommodative esotropia is well established and various side-effects are recognized.[1]

Ciliary and iris sphincter spasm leading to brow pain, photophobia, and induced myopia may occur early. Also noted in the first few days of treatment are conjunctival hyperemia and congestive iritis. A commonly observed complication is the formation of iris pigment cysts, especially after prolonged daily use of DFP in children, though the exact mechanism remains uncertain. These cysts usually regress and disappear after reducing the frequency of administration or discontinuing the drug.[2, 3]

As far as can be ascertained from a survey of the literature toxic effects on the lens have not been described in humans or in experimental animals. In one extensive experience of experimental use of DFP for 14 years, no such lenticular changes have been reported.[4] The following case indicates that lenticular opacities may occur and illustrates what appears to have been the formation of bilateral reversible lens opacities. The orthoptic and refractive measurements are omitted.

Case report

A girl, aged 13 years, was treated at the Ocular Motility Clinic of the Boston City Hospital in November, 1958, for esotropia in which an accommodative element was elicited. She was given a well-known proprietary preparation of DFP ophthalmic solution (0.025 percent in peanut oil), one drop being instilled in each eye every night. Vision at this time was 20/20, O.U., with the proper refractive correction. Routine systematic examination of the anterior segments with the slitlamp microscope was made three weeks later. This examination was normal though it was noted that the degree of miosis was not extreme and a slight pupillary light reaction was still present. There was considerable improvement in the esotropia.

The patient was examined each month thereafter. In February, 1959, after three months of continuous treatment, no iris cysts had been observed but a striking, silvery-gray, delicate and complete rosette formation of petals, tracing the fine feathery architecture of radiating lens fibers was seen in the anterior subcapsular region of each lens. This finding was confirmed by several competent observers. There were no signs of uveitis or any other abnormality. No appreciable change was noted when the patient was seen again in March, although at this time a typical pigment cyst had developed at the pupillary margin in each eye. Vision had not altered but it was decided to discontinue the use of DFP.

After nine days it appeared that the lens opacities were less pronounced on slitlamp examination and examination three weeks after the cessation of the DFP showed complete disappearance of the subcapsular rosette patterns. Slitlamp examination every fortnight subsequently for two months, failed to reveal any recurrence and throughout the whole period the patient's vision remained unaffected.

Following the withdrawal of DFP, the esotropia recurred. There were no other manifestations of DFP irritation and no conjunctival follicles or allergic reactions were found. It was considered inappropriate to attempt to reproduce the condition by unilateral administration of DFP.

Comment

It is highly unlikely that the formation of iris cysts was responsible for the changes because the former are not uncommon. Moreover, a ciliary body tumor compressing the lens does not readily cause opacification of the lens.

The manufacturers do not produce 0.025-percent DFP solution in peanut oil, though an experimental preparation of this strength in sesame oil is available. Local pharmacists have diluted the usual 0.1-percent solution in peanut oil to the prescribed concentration. The actual specimen of DFP solu-

* From the Eye Service and the Ocular Motility Clinic, Boston City Hospital, Boston, Massachusetts.

tion used in this case was not obtained for toxicologic analysis and the possibility of chemical contamination by an unknown substance cannot be ruled out.

It is noteworthy, in comparison, that human cataracts following the systemic use of dinitrophenol given for obesity have been described as commencing in the anterior subcapsular layer as vacuoles and powdery fine opacities in only 0.1 to 1.0 percent of persons who used the drug as a remedial agent. Only in the later stages were denser, bronze, posterior cortical irregularities described.

It is also of interest that, in some instances of concussion cataract taking the form of similar anterior subcapsular rosette formations, complete clearance occurred in the course of several days or weeks. It is thought that in such cases the lens fibers had not been irreversibly damaged while the carpet of fluid droplets which produce the feathery appearance is absorbed completely.[5]

It is characteristic of these milder concussion changes in the anterior subcapsular layer that vision is hardly impaired and this fortunate feature was present in our case.[6]

There is some opinion that prolonged use of miotics in treating glaucomatous eyes has led to cataract formation. Pilocarpine in topical application has been shown to inhibit respiration in the rabbit lens.[7]

Di-isopropryl fluorophosphate is a powerful chemical irritant and is quite stable in peanut oil. Possibly hydrofluoric acid and elemental fluorine are released in the aqueous as a result of hydrolysis. The fluorine ion diminishes tissue respiration and anerobic glycolysis in excised organs. It is not, however, the intention of this brief report to speculate on cataractogenic mechanisms.

It is considered probable, though not proven, that the individual described showed a susceptibility to DFP manifested by the formation of toxic lens opacities. No other patients attending the Ocular Motility Clinic, receiving similar therapy, showed lenticular changes. This patient was in good health and had no skin complaints throughout the period of observation.

243 Charles Street (14).

ACKNOWLEDGEMENTS

I wish to thank Dr. W. Morton Grant of the Massachusetts Eye and Ear Infirmary for his valuable criticism and Dr. D. Robert Alpert, Chief, Department of Ophthalmology, Boston City Hospital, for his helpful comments and advice. The collaboration of Miss Mary Heffernan, orthoptic technician, Boston City Hospital, is gratefully acknowledged.

REFERENCES

1. Knapp, P., and Capobianco, N. M.: Use of miotics in esotropia. Am. Orthoptic J., **6**:40, 1956.
2. Malbran, E. S., and Norbis, A.: D.F.P. in the treatment of convergent strabismus. Ann ocul., **188**: 720 (Aug.) 1955. (Abstract in Am. J. Ophth., **41**:1091 [June] 1956.)
3. Swan, K. C.: Iris pigment nodules complicating miotic therapy. Am. J. Ophth., **37**:886 (June) 1954.
4. Sherwood, J. M.: Personal communication. May, 1959.
5. Duke-Elder, W. S.: Textbook of Ophthalmology, London, Kimpton, 1954, v. 6, p. 5811.
6. ———: Textbook of Ophthalmology. London, Kimpton, 1954, v. 6, p. 5814.
7. Müller, H. K., Kleifeld, O., Hockwin, O., and Dardenne, U.: The influence of pelocarpine and mintacol on the metabolism of the lens. Deutsch. Ophth. Gesellsch., **60**:115-120, 1956.

WILLIAMS' PRIOR DESCRIPTION OF MARFAN'S SYNDROME*

DORRANCE BOWERS, M.D.
Kelowna, B.C., Canada

In 1896, A. B. Marfan,[1] a Parisian pediatrician, reported in detail the case history of a five-and-a-half-year-old girl with long slender extremities and a marked degree of dolichocephaly. He stated that his patient's eyes and internal organs were normal and that there was no family history of skeletal abnormalities similar to those of the patient.

Since the appearance of this report, additional abnormalities have been associated with these skeletal anomalies. For example,

* From the Knox Clinic and Kelowna General Hospital.

the ocular lenses may be dislocated and saccular or dissecting aortic aneurysms may develop. Also, it has been shown that this constellation of abnormalities may be transmitted from one generation to the next as a dominant characteristic. To this syndrome, the name of Marfan has become attached. Thus, we speak of "Marfan's syndrome" or "the Marfan syndrome."

The purpose of this paper is to draw attention to an earlier and more complete description of the syndrome than that of Marfan. In 1876, Elkanah Williams,[2] an ophthalmologist in Cincinnatti, described four patients with dislocated ocular lenses. Of these, a brother and sister, Mary J. and Marcus J., were almost certainly afflicted with what is now known as Marfan's syndrome. The following paragraphs are quoted from Williams' paper:

> The two following cases of spontaneous luxation of the lenses, also in brother and sister, present some points worth reporting. Mary J., aet. 28, single, consulted me July 17, 1875. Eyes slightly divergent, pupils small and slugglish, irides trembling, and of a bleached, dirty gray color; chambers deep. Her eyes have been about equal till within the past few weeks, when she noticed a glimmering before the right, and a curtain dropped down from above, nearly cutting off all vision. All qualitative perception is abolished in the field of vision, except below where she counts fingers near the floor at three feet. Eye slightly injected, and sensitive to light and touch; tension 1, and she complains of the constant glimmering before that eye.
>
> Pupil small, central and round, but does not dilate much with atropine. The lens, semi-transparent, is dislocated *upwards*, leaving about one-fourth of the pupillary area clear. The lower edge tilts backwards in vitreous, while the upper seems to rest against iris and push it slightly forward. With ophthalmoscope, red reflex above, but bluish-gray appearance below, indicating detachment of the retina; fundus invisible.
>
> L. e. luxation *upwards*, and two-thirds of pupil free. Lens transparent, but appears small, the lower edge also presenting backward, and the upper pushing iris slightly forward. No double vision. V. = 15/200, and with + 7 = 15/40. She reads Snellen 1 with + 4½ at six inches. Could see fundus dimly; but as I did not wish to put anything in this eye atropine was not used. The father's eyes were like theirs, but their mother and only brother had good eyes. In her right eye the irritation and detachment of the retina came on without trauma, confirming the well-known fact that all such eyes are liable to blindness from disease of fundus, and especially from detachment of the retina. The patient says she has always been a great reader by the aid of glasses, which she did not have with her. He brother, Marcus J., aet. 26, large and *loose-jointed* like his sister, brought her to see me, but had *Nothing* the matter with his eyes, always having seen *Perfectly*, as he declared. A marked divergence of his eyes and their peculiar expression attracted my attention, and I noticed that he stuttered. On inspection I found the same deep chambers, trembling irides, pupils small and central, but pear-shaped; the points presenting downwards, and sluggish. L. e. V. = 15/100, and improved to 15/20 + with + 7. R. e. V. = 15/200 and 15/50, with +7. Divergence three lines, the patient fixing usually with the left eye, with which he reads Snellen 1 with + 4½. Both lenses are displaced upward, the right slightly inward. When eyes are horizontal the lower edge of each lens comes below the centre of the pupil, but he has no diplopia. Lenses a little hazy and reduced in size. Field of vision perfect in both eyes.

Biographical details concerning Williams have been extracted from a long obituary notice written by Sattler.[3] Williams, who was born on December 19, 1822, in Lawrence County, Indiana, received the degree of M.D. from the University of Louisville in 1850, and then engaged for 18 months in the practice of general medicine. After three years of postgraduate study in ophthalmology in Europe, he established a practice in his specialty in Cincinnati. Later, at Miami Medical College, he became the first professor of ophthalmology in the United States. His numerous contributions to American and foreign medical journals brought him wide renown. He retired from practice in 1886 because of ill-health and died on October 6, 1888.

While it is likely that Marfan's name will continue to be attached to "his" syndrome, this resurrection of the prior description may obtain for Williams further well-deserved recognition.

426 Lawrence Avenue.

ACKNOWLEDGMENTS

I am indebted to Miss Sheila Blackie, Medical Record Librarian, Kelowna General Hospital, and to Miss Mary E. Grinnell, National Library of Medicine, Washington, D.C., for bibliographical assistance.

REFERENCES

1. Marfan, A. B.: A case of congenital deformation of the four limbs, more marked at the extremities, characterized by lengthening of the bones with a certain degree of thinning. (Translation). Bull. Mém. Soc. Med. Hôp. Paris, **13**:220, 1896.
2. Williams, E.: Rare cases, with practical remarks. Tr. Am. Ophth. Soc., **2**:291, 1876.
3. Sattler, R.: Dr. E. Williams. Tr. Am. Ophth. Soc., **5**:237, 1889.

SIMPLE MODIFICATION OF SYNOPTOPHORE

USEFUL IN PLEO-ORTHOPTIC TREATMENT

ALFREDO ARRUGA, M.D., AND

RACHEL DOWNEY, D.B.O.

Barcelona, Spain

The aim of the following lines is to show to those colleagues who are interested in the present tendencies of pleo-orthoptic treatment how it is possible to adapt to practically any synoptophore easy-to-make modifications incorporating all the necessary adjuncts proper to the modern treatment of amblyopia and anomalous retinal correspondence.

In orthoptic treatment one feels more at ease when working with the apparatus that one is accustomed to; this facilitates enormously the execution of the treatment.

Recently, the treatment of monocular and binocular anomalies encountered in strabismus has been the object of some interesting innovations, particularly that concerning eccentric fixation and the alterations of the sensorial relationships. This is mainly due to the researches of Prof. Cüppers, of Giessen.

One of the most significant contributions of this author has been the utilization in pleoptic and orthoptic treatment of afterimages, the possibility of creating them being incorporated in most synoptophores today. Another is the well-known phenomenon discovered by Haidinger, an Austrian mineralogist, in 1844, the "Polarization Bueschel"—Haidinger's brushes; this phenomenon is strictly macular and is recognized as having the character of an "object."

In order to make this phenomenon continuously visible, a light source of sufficient strength, a constantly rotating polarizator and a special blue filter are necessary.

Fig. 1 (Arruga and Downey). Rotating unit with socket for polarizating slide and motion slides.

In 1950 Goldschmidt introduced a device for detecting the function of the macula and proposed it as a prognostic test in cases of amblyopia.

The first pleoptic adaptation of Haidinger's brushes was the table "Koordinator,"

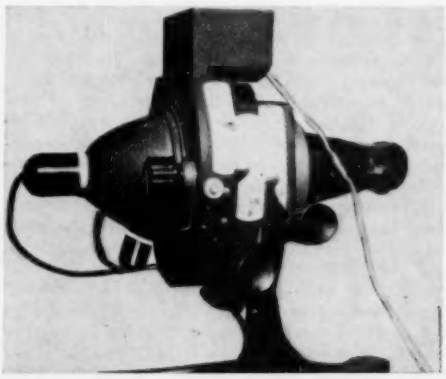


Fig. 2 (Arruga and Downey). Rotating unit in position in the space behind the slide carrier in a synoptophore.

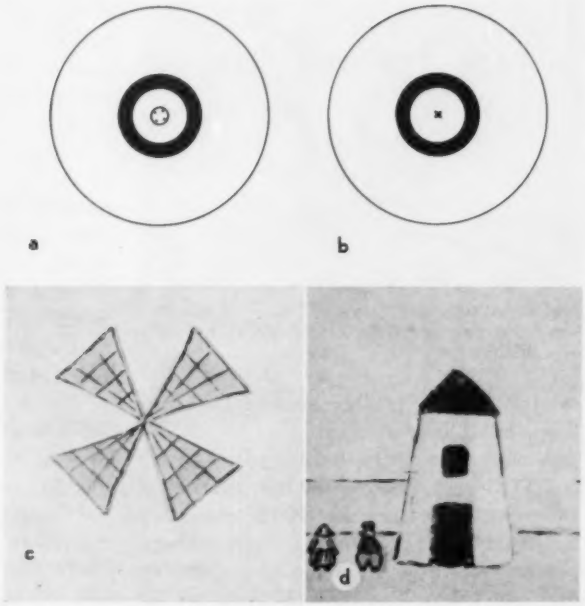


Fig. 3 (Arruga and Downey). Examples of motion slide images to be used together (a, b,) or combined with immobile pictures (c, d,).

made by the German firm "Oculus." This has also been adapted for use in space. A Haidinger's-brushes device is likewise incorporated in the "Oculus Synoptophor."

We have constructed for the amblyoscope a simple Haidinger's-brushes device which consists of a rotating polariod disc (No. 328 polaroid film) driven by a four to nine volt Micron electric motor. This motor* has been selected owing to its five division collector permitting an extremely regular rotation even at low speeds.

The ordinary illumination of the synoptophore being insufficient (unless fitted with a special after-image light source, adapted to

Fig. 4 (Arruga and Downey). Showing additional lamp carrier for strong illumination necessary to the Haidinger's-brushes unit and an iris diaphragm slide in position. This is used in combination with specially constructed thin slides. Double filament lamps (one filament being connected to a flashing device) allow use of "euthyscopic" after-images and Haidinger's brushes in synoptophore monocular treatment.

* Made by Moteurs Micron, 8, Passage de Ménilmontant, Paris 11, France.

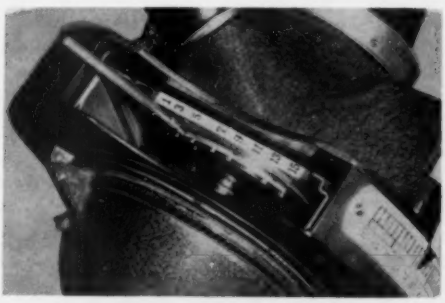


Fig. 5 (Arruga and Downey). Detail of iris diaphragm in slide carrier. Figures indicate the degrees of aperture.

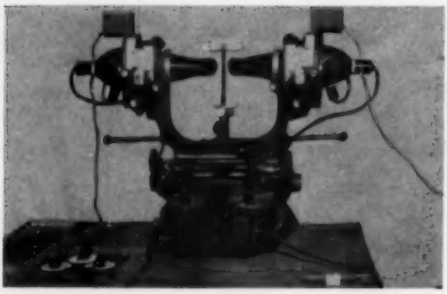


Fig. 6 (Arruga and Downey). View of synoptophore with two motion-slide Haidinger's-brush units in position.

several models recently) additional 20 watt lamps have been installed.

A blue-violet filter—for example Corning No. 5113—not allowing the transmission of wavelengths greater than 490 μμ, can either be placed in the amblyoscope's cell for supplementary lenses or in the space between the light source and the polarizator in the slide carrier. Another blue-violet filter of specific density, according to the stage of treatment, is placed before the sound eye.

In the Haidinger's-brushes device the rotating slide containing the polarized filter can easily be removed from the socket where it fits by pressure. This has been done in order to be able to change the polaroid slide for other motion slides, especially designed for antisuppression exercises. These can be used either with ordinary immobile fusion slides or combining two motion slides to work simultaneously, one for each eye.

Mobile images are of great anti-inhibitive power and so here the idea is to present actual continuous movement, and not a succession of immobile images, as occurs in the phi phenomenon, either monocularly or binocularly.

Cüppers has emphasized the importance of the decreasing field method in the treatment of the anomalies of localization, using after-images, Haidinger's brushes and real objects, in eccentric fixation. We will not go into the particulars of this method here, which have been described in detail by Cüppers elsewhere, the interested reader being referred to his articles.

The introduction of a decreased field slide into the synoptophore has the disadvantage of interfering with the vision for a moment, this may be sufficient for the patient to loose the Haidinger's-brushes, who may find it difficult to localize them again. This can be easily avoided by using a decreasing field slide, improvised with an iris-diaphragm, adapted to a plastic plate, introduced in the amblyoscope's slide carrier.

Summary

A device for using rotating slides as an antisuppression exercise in the synoptophore is described. This device can also be fitted with a rotating polarizator, plus a blue-violet filter, for creating Haidinger's brushes. This is the phenomenon which Cüppers has utilized for the treatment of eccentric fixation amblyopia. The decreasing field, used also in this treatment, is obtained by means of an iris diaphragm.

Pasaje Mendez Vigo 3.

References

Cüppers, C.: Klin. Monatsbl. f. Augenh., **128**:236, 345, 353, **129**:579, 1956; Klin. Montasbl. f. Augenh., **133**:437, 1958; Orthoptic problems in Germany (Lectures at Leeds and Sheffield); Egozentrische Lokalisation und Lokalisationswandel (Lecture at Barcelona).

Downey, R.: Brit. Orth. J., **15**:36, 1958.

Goldschmidt, M.: Arch. Ophth., **44**:129, 1950.

Haidinger, W.: Ann. Phys. Chem. (Lpz.), 1844-54. (Quoted by Downey).

Sloan, L. L., and Naquin, H. A.: Am. J. Ophth., **40**:393, 1955.

Stanworth, A., and Naylor, E. J.: Brit. J. Ophth., **34**:262, 1950.

USE OF MILLIPORE FILTERS IN OPHTHALMIC SURGERY*

ROBERT C. DREWS, M.D.
Saint Louis, Missouri

The occasional biomicroscopic observation of particulate "debris" in the anterior chamber of patients after cataract surgery is annoying, but the surgeon is consoled by the usual lack of reaction to this material. After a lamellar corneal transplant, the presence of debris between the transplant and the recipient cornea can give rise to a haze at this interface which may spoil an otherwise excellent result. Forbidding the use of cotton swabs helps but has not been sufficient to eliminate this complication. One of the most obvious sources of this material in operating rooms is the saline used for irrigation. The debris itself arises from the sterile linens, from rubber irrigation bulbs and from dust in the operating room air, as examples. Some of these sources are likely to be contaminated with bacteria.

Millipore filters are widely used in industry to remove particles from gasses and fluids, and in microbiology to collect bacteria quantitatively. The use of millipore filters in the operating room permits both the study and the elimination of material from irrigating solutions.

MATERIALS AND METHODS

Millipore filters are cellulosic membranes, 150 microns thick, having approximately 50,000,000 capillary pores per square cm. of filter surface. The pores constitute 80 percent of the volume of the filter. These pores are remarkably uniform in size: the HA grade used in this work has pores

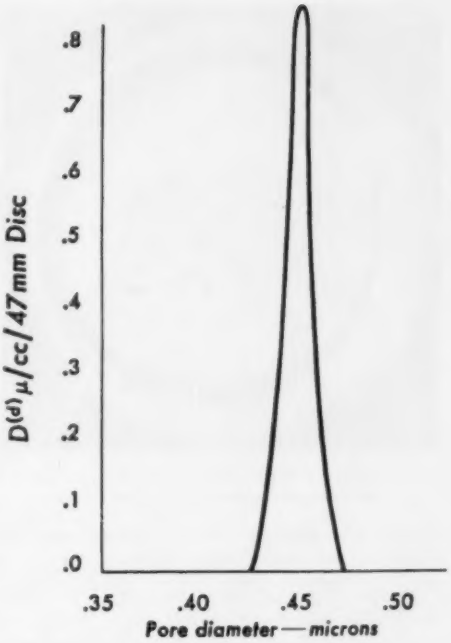


Fig. 1 (Drews). Millipore filter pore size distribution (Skau-Ruska mercury intrusion).

0.45± 0.02 microns (fig. 1). This size was chosen because it is small enough to filter out not only particulate matter but also all bacteria. Smaller sizes (down to 0.010 microns) are available, but we were not interested in virus filtration, and perferred the better flow rate afforded by the larger pore size. Filters were mounted in Swinny adapters and autoclaved. It was found that excessive autoclaving led to rupture of the filters (fig. 2); a given filter is now autoclaved only once and no longer than 20 minutes. It was also found advisable to have the system dry before autoclaving.

Broth suspensions of Staphylococcus aureus were used for a control. The organism grew confluently on the filters, and the filtrate was found to be entirely sterile. Further controls consisted of examining filters through which nothing had been filtered, and through which saline was filtered directly from the intravenous bottles.

---

* From the Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine.

This investigation was supported in part by a research grant, B-1375, from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service, Bethesda, Maryland.

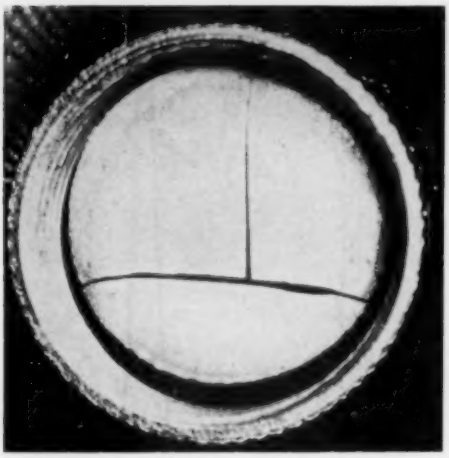


Fig. 2 (Drews). This millipore filter was autoclaved 20 minutes on seven successive days.

Rare tiny particles were present on the filters after autoclaving without filtration. Particle counts from intravenous saline averaged four particles per cc.

Results

Filtration of irrigating solutions led to the recovery of more debris than anticipated (fig. 3). Counts were made with 50-power magnification, and ranged from 453 to 958 particles per ml. Fluid was not taken from the surface of the jars of irrigating saline, where particulate matter could be seen floating, but from the depths. Encouragingly however, in filtration of 14 jars of saline after various operative procedures, no bacteria were recovered which could be grown on nutrient broth.

The most prominent type of particle seen without magnification was lint. There were only 10 to 20 particles per cc., however. Interestingly, many of these pieces of lint were dyed green at least in places: our drapes are also dyed green. The smaller particles were mostly sand (that is, yellow and clear, irregular, glassy grains) and dirt (that is, amorphous black specks). Rarely, metallic fragments and crystals were found. Rubber fragments were seen after use of an irrigating bulb.

Fig. 3 (Drews). Debris from 0.5 cc. of irrigating solution, as collected on the surface of a millipore filter.

For clinical use in the operating room the filters are mounted with wire screen supports on both sides to prevent accidental rupture by improper use. Because flow rates are too small for direct irrigation, we prefer to have the nurse draw solutions through the filter into a glass syringe. The filter is then removed and a metal cannula placed on the syringe. Rubber bulbs are avoided, as they form a source of debris.

The same filter system can be used to sterilize air for injection into the anterior chamber or orbit. The filter must be dry. Millipore filters are also useful for sterilizing eyedrops.*

Summary

Millipore filters can be used to advantage by the ophthalmic surgeon in the preparation of irrigating solutions, for both their cleansing and sterilizing effect.

640 South Kingshighway (10).

* Riegelman, S., Vaughan, D. G., Jr., Okumoto, M.: Compounding ophthalmic solutions. J. Am. Pharmacol. A., **16**:742-746 (Dec.) 1956.

RETINAL LESIONS IN KALA-AZAR

WILLIAM S. TASSMAN, M.D.
Philadelphia, Pennsylvania
DAVID D. O'BRIEN, M.D.
AND
KURT HAHN, M.D.
Wiesbaden, Germany

Leishmania donovani, a protozoon parasite, was discovered in 1900 by Sir William Leishman.[1] In 1903, Donovan confirmed the discovery and helped to establish the organism as the etiologic agent of kala-azar, a chronic infection which shows a special affinity for the reticulo-endothelial system.[2]

The parasite is found in two forms during its life cycle. In man it is about three microns long, oval, and without flagella. In insects it is 12 to 14 microns long, and prominent flagella are present.

The disease is endemic in Asia, Africa, and the Mediterranean area. It is transmitted by the phlebotomus sandfly.

Characteristically the most common symptoms of kala-azar are intermittent or remittent fever, anorexia, malaise, and occasionally purpura and bleeding from the nose or gums. Physical findings include fever, hepatosplenomegaly, and lymphadenopathy, while examination of the blood shows a macrocytic hyperchromic anemia and leukopenia. Hyperglobulinemia may also be present.

While the above classical features of kala-azar have been amply described in the literature, no mention is made of retinal lesions. The case presented here is of interest because superficial retinal hemorrhages and cytoid bodies were noted.

CASE REPORT

F. F., a 30-year-old white man stationed in Madrid, Spain, was well until the evening of January 12, 1959, when he developed a fever. The fever subsided spontaneously in a few hours but was followed thereafter by daily spikes, usually in the late afternoon. After one week the patient became anorexic. He reported to his local hospital where a fever of 103.6°F. was noted. The pulse was 100, and on physical examination the liver edge was palpated 3.5 cm. below the right costal margin. The spleen and axillary nodes were also palpable.

A hemogram revealed 2,300 leukocytes with 48 percent neutrophils and 52 percent lymphocytes. Hemoglobin was 9.4 gm.

Malarial smears were negative but a gram-negative rod was cultured from the blood. On the basis of the findings, typhoid fever was suspected and, on January 24, 1959 chloramphenicol and penicillin therapy was started. Despite treatment daily fever spikes to 104-105°F. continued.

Because of a continuing drop in red and white cells, blood transfusions were given on January 25, 1959, February 5, 1959, and February 7, 1959.

On February 9, 1959 the patient was transferred to the U.S.A.F. Hospital, Wiesbaden, Germany.

General physical examination at that time showed a well-developed, thin, white male, appearing chronically ill and pale. Blood pressure was 130/84 mm. Hg; pulse 96, temperature 101°F. The skin was smooth and warm. No spiders or petechiae were noted. With the exception of the eyes, examination of the head and neck was not remarkable. The lung fields were clear. The PMI was just outside the left midclavicular line in the fifth intercostal space. A soft Grade 2 blowing apical systolic murmur was present. The abdomen was distended with a prominent venous pattern. The liver was palpable seven cm. below the right costal margin. It was smooth and tender. The spleen was palpable six cm. below the left costal margin but was not tender. Examination of the lymphatics revealed palpable axillary and posterior cervical nodes. The extremities had no palpable edema. The nails were pale. Genital, rectal, and neurologic examinations were not remarkable.

Eye examination. Visual acuity was: O.D., 6/6 without correction; O.S., 6/6 without correction. Intraocular pressure was: O.D., 17 mm. Hg; O.S., 17 mm. Hg (Schiøtz).

External examination. The lids, cilia, lacrimal drainage apparatus, conjunctiva, and corneas were all normal. The anterior chambers were of normal depth and clear. The iris was normal in both eyes. The pupils were round, equal, and reacted to light directly and consensually.

Muscle balance was normal.

Fundus examination showed the media to be clear in both eyes. The discs were of good color with distinct margins. The veins were slightly dilated and a vascular sheathing was noted. Macular reflexes were good. Superficial retinal hemorrhages were present in both eyes. In the right eye two white spots about one-quarter disc diameter in size were seen just nasal to the disc. A larger white spot about one-half disc diameter in size was located superficially in the retina temporal to the disc in the left eye (fig. 1). Because of the appearance, location in the posterior portion of the fundus, and the generalized toxemia of the patient, these lesions were thought to be cytoid bodies.

Laboratory studies. Complete blood count showed

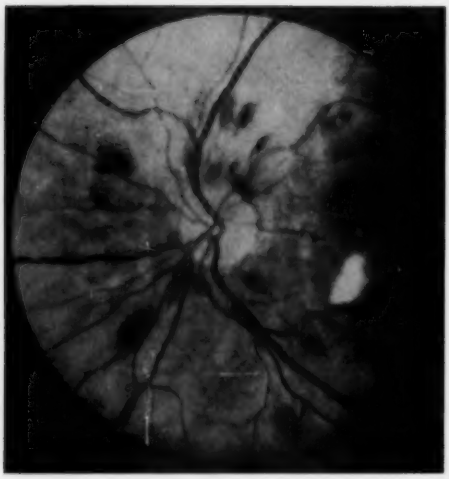


Fig. 1 (Tassman). Appearance of fundus of left eye before therapy was started.

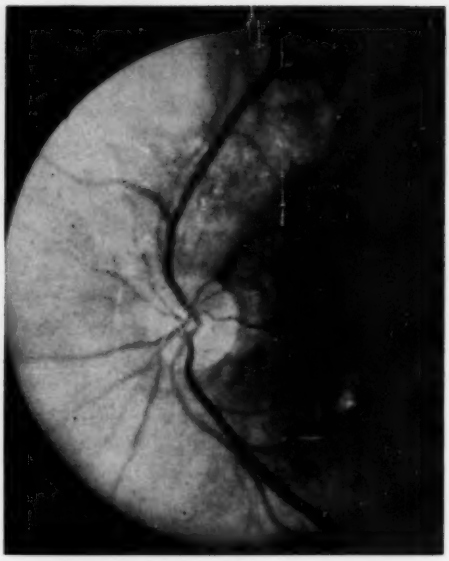


Fig. 2 (Tassman). After stilbamidine therapy was started the superficial retinal hemorrhages and cytoid bodies began to resolve.

a hemoglobin of 9.4 gm.; white blood cell count 5,900; differential count was segmented neutrophils 65 percent, lymphocytes 34 percent, and monocytes one percent. Total serum protein was 5.8 gm., albumin 3.4, globulin 2.4. Bilirubin was 0.56 mg. percent, thymol turbidity 9 units, and cephalin flocculation 3+ after 48 hours. Fasting blood sugar was 95 mg.; sedimentation rate 17 mm. in 60 minutes. Lee and White coagulation time: 8 min., 40 sec., bleeding time 2 min., 15 sec. Serum protein electrophoresis revealed elevation of the alpha globulin and gamma globulin. Albumin was moderately depressed. Malarial smears and a preparation for lupus erythematosis were negative.

Urinalysis was normal. Stool examinations for ova and parasites were not remarkable.

Impression. At this point it was felt that there was strong evidence to indicate diffuse involvement of the reticuloendothelial system, possibly by a parasitic infestation. A bone marrow aspiration was therefore done but no parasites were found. On February 19, 1959, a liver biopsy was performed and many leishmania were discovered in the parenchymal cells.

On February 20, 1959, 2-hydroxy-stilbamidine, 225 mg. per day intravenously, was started. The patient had been acutely febrile with a double spiking fever throughout his hospitalization. Two days after starting stilbamidine therapy a gradual decrease in the spikes began. By March 1, 1959, no more fever was present.

The superficial retinal hemorrhages and cytoid bodies began to resolve (fig. 2). The liver, spleen, liver function studies, hemoglobin, and white blood cell count returned to normal. On March 13, 1959, a repeat liver biopsy revealed no leishmania. Therapy with stilbamidine was discontinued on March 27, 1959, after a total dose of 7,875 mg. over a 35-day period had been given. Since his discharge the patient has remained asymptomatic and presents no abnormalities on either physical examination or laboratory study.

Discussion

Cytoid bodies should not be regarded as pathognomonic of any particular disease. They are a manifestation of a generalized toxemia. Roth,[4] in 1872, was the first to make this observation. Since that time cytoid bodies have been noted in the nerve-fiber layer of the retina in such conditions as acute lupus erythematosis, hypertension, leukemia, increased intracranial pressure with papilledema, and optic neuritis.[4] As illustrated in this case, they are not prognostic of a fatal termination. If control of the generalized disease can be accomplished complete resolution may be expected.

Summary

A case of proven kala-azar has been presented. In addition to the classical features of the disease, retinal lesions were noted.

Many superficial retinal hemorrhages and three cytoid bodies were present. On stilbamidine therapy the general condition of the patient markedly improved, and the retinal picture returned to normal.

1601 Spring Garden Street (30).

REFERENCES

1. Cordero, A. A., and Corti, R. N.: Leishmaniosis. La Prensa Med. Argentina, **40**:3467-3472, 1953.
2. Cecil, R. L., and Loeb, R. F.: Textbook of Medicine. Philadelphia and London, Saunders, 1951, pp. 394-401.
3. Pestre, A.: Manifestations oculaires de la Leishmaniose cutanee. Algerie Med., **59**:589-597, 1955.
4. Maumenee, A. E.: Retinal lesions in lupus erythematosis. Am. J. Ophth., **23**:9, 1940.

HYPNOSIS AS AN ANESTHETIC IN OPHTHALMOLOGY*

OTHON R. GÓMEZ RUIZ, M.D., AND ANTONIO FERNÁNDEZ, M.D.
Havana, Cuba

Hypnosis was used as an anesthetic in the following case.

CASE REPORT

Mr. R. R., white, aged 36 years, had an intumescent cataract, his vision being 20/500 in both eyes. All preoperative tests were favorable as well as the local condition of the eyes (light projection, motor reflexes, intraocular pressure, and so forth).

On January 24, 1959, the left eye was operated. Upon the application of one-percent pantocaine and retrobulbar injection of two-percent Novocaine, the patient showed an alarming degree of dyspnea, profuse lipothymia, with a blood pressure of 70/60 mm. Hg. The operation was interrupted and emergency treatment applied. After investigation, it was concluded that the patient was sensitive to all local anesthetics. In view of this we decided to use general anesthesia.

On February 10th, surgery was again attempted. The patient was a tall, heavy man with a short and thick neck and serious technical difficulties arose when the anesthetist tried to insert the tube in the trachea. Three attempts failed. During the second and third attempts, the patient became cyanotic, with marked respiratory difficulty. Since a fatal outcome or the possibility of central nervous system damage from anoxia was feared, we decided not to proceed with surgery this time either.

Acknowledging the impossibility of desensitizing for anesthetics, we decided to operate with the patient under deep hypnosis.

On May 19th, the first preoperative hypnotic session was started and continued at four-day intervals for three sessions. A deep trance was obtained, with anesthesia at superficial and deep levels.

On June 10th, the patient was admitted to the hospital. The following day he was put under hypnosis in the operating room without any preoperative sedation (drugs). Five minutes later surgery was started.

The operation was conducted in the ordinary manner (corneal incision, scissors, iridectomy, eight sutures). The patient appeared completely relaxed and in good general condition, showing a complete loss of sensibility but preserving the oculomotor reflexes. At the end of the operation, when he was awakened, he showed no signs of pain or discomfort (due to the posthypnotic suggestions). The patient was under hypnosis for a total of 25 minutes.

On June 20th, 10 days after the operation, vision was 20/40 with a +10D. sph. On July 26th, vision was 20/20, J1.

L No. 452, Vedado.

* From the League Against Blindness Hospital and Covadonga Hospital.

We wish to thank Dr. Tomás R. Yanes, Director of the League Against Blindness Hospital for his encouragement.

GLAUCOMATOCYCLITIC CRISES

DEREK G. SIMPSON, F.R.C.S.
(Eng. and Edin.)
Vancouver, British Columbia

REVIEW

Glaucomatocyclitic crises were first named and described as a clinical entity by Posner and Schlossman in 1948.[1] Earlier literature contains vague or incomplete descriptions of conditions which might have been glaucomatocyclitic crises.[2-5] The condition soon attracted attention and recognition. Papers by several American authors[6-9] have appeared and cases have been reported from other countries.[10-14] The incidence is difficult to determine because more cases

will be recognized when the characteristics of the condition become more widely known.

Etiology

Posner and Schlossman[15] are noncommittal about the etiology. Grant[16] showed reduced aqueous flow during attacks in three cases but in remissions greater or normal flow. No structural changes can be detected between attacks. Allergy is suggested as a causative factor by Theodore[10] and Kornzweig[7] wonders if it could be angioneurotic edema of the eye. Burton[17] reports association with the common cold, while Rud[18] reports mild tonsillitis associated with several of the attacks in one case.

In the case here reported nervous tension may be an etiologic factor. Of the six attacks in this case, four occurred when the patient was working under tension as a salesman by day and a band player at night. One attack followed one and one-half hours after a car accident, and one attack when worrying about a change of job.

Posner and Schlossman[19–22] give an excellent description which is here summarized:

Classification of glaucoma associated with cyclitis:

1. Iridocyclitis occurring in a person with primary glaucoma—very rare.
2. Mild iridocyclitis with hypertension early: (a) recurrent glaucomatocyclitis crises; (b) iridocyclitis without posterior synechia (or old synechia) associated with early appearance of hypertension.
3. True secondary glaucoma resulting from iridocyclitis: (a) early, active iridocyclitis with plasmoid aqueous, new posterior synechia, and so forth; (b) late, associated with structural changes in the filtration channels or with long-standing uveitis.

Criteria of glaucomatocyclitic crises:

1. It is always unilateral and in the same eye.
2. The tension is higher than the mild symptoms or degree of cyclitis would suggest: (a) the tension is usually about 40 mm. Hg but may be 70 mm. Hg or more; (b) the eye is white; (c) the vision is normal or only slightly blurred (if the tension higher). It is rarely less than 20/40; (d) pain is absent or insignificant.
3. The pupil is wider during attacks, anisocoria may persist between attacks.
4. The cyclitis is mild. Keratic precipitates are not numerous and may be concealed by corneal edema (use Pontocaine then glycerine drops to clear the cornea). The keratic precipitates are small, round, flat and not pigmented. They fade in one to four weeks. Only a trace of flare is seen and posterior synechia never occur.
5. The filtration angle is open.
6. The course of an attack is characteristic: (a) the tension becomes normal spontaneously in one to 14 days; (b) keratic precipitates appear in one to three days and disappear in one to four weeks.
7. The prognosis is good despite repeated attacks: (a) provocative tests are normal; (b) fields remain normal; (c) cupping of the disc does not develop; (d) attacks vary in frequency without apparent cause.

Treatment

Mild miotics (pilocarpine, 0.5 to 2.0 percent) and cortisone drops are advised during attacks. Repeated dilatation with an epinephrine compound is desirable to give reassurance that no synechia are forming. Diamox is helpful. Surgery, including paracentesis, is not desirable during attacks. The attacks are self-limiting and recovery is perhaps as rapid without treatment. Pain and congestion are more evident if treated with strong miotics. Between attacks no treatment is desirable. Pilocarpine will not prevent attacks nor will iridectomy or fistulizing operations.

Differential diagnosis

1. Acute narrow-angle glaucoma has a narrow angle, shallow anterior chamber, pain, congestion and severe drop in vision. Provacative tests are positive.

2. Glaucoma secondary to iridocyclitis has posterior synechias, pigmented keratic precipitates, more flare, small pupil, and so forth.

3. Glaucomatocyclitic crises have unilateral (same eye each attack) dilated pupil, no synechias, fine keratic precipitates, only a slight blur of vision. Tension is high compared to mild symptoms.

Case report

Mr. R. M., aged 42 years, a salesman and dance band player has always had this condition in the left eye, never the right. During the course of two years he had three attacks of seeing halos and slight discomfort, always when he had been working very hard (day and night). The attacks responded fairly promptly to drops for glaucoma prescribed

by an ophthalmologist in another city. For the last three years he had been free of attacks—and not playing in dance bands very often. In December, 1955, he had busy days selling and worked most evenings with dance bands. He also had a 30-mile drive in traffic to and from work. I first saw him December 13th, during an attack.

Examination showed: O.S., mild injection, tension 46 mm. Hg, corneal edema, deep anterior chamber. In spite of glycerine being employed no keratic precipitates were seen. Pilocarpine (four percent) was given. The tension fluctuated between 31 and 24 mm. Hg for 10 days and a few fine keratic precipitates were seen. Suddenly the tension fell to 12 to 14 mm. Hg with disappearance of symptoms and the few fine keratic precipitates. The fields were normal. The tension did not rise when pilocarpine was stopped and a dark-room test was negative. Pilocarpine (two percent) night and morning was prescribed.

On February 15, 1957, there was a recurrence of halos in spite of using pilocarpine. This attack followed one and one-half hours after a car accident. He had used pilocarpine drops several times before I saw him. O.S. showed mild injection, no corneal edema, no keratic precipitates, and a tension of 25 mm. Hg. A few fine keratic precipitates were seen two days later. The attack was completely over in a week. No posterior synechias formed. Following this attack the patient has used no drops and the tension has remained between 14 and 18 mm. Hg. He presented with another attack on May 23, 1958, seeing halos in O.S. There were three fine keratic precipitates; tension 37 mm. Hg. He admitted worrying about a possible change of job. On May 26th, tension was: O.S., 30 mm. Hg, no keratic precipitates; May 30th, O.S., tension 15 mm. Hg. No attacks have occurred since then.

Summary

Glaucomatocyclitic crises are briefly reviewed, classified, and described by Posner and Schlossman's criteria. The treatment and differential diagnosis are summarized. A case is presented which suggests that nervous tension may be an etiologic factor.

622 Medical-Dental Building (1).

References

1. Posner, A., and Schlossman, A.: Arch. Ophth., **39**:517 (Apr.) 1948.
2. Streiff, J.: Klin. Monatsbl. f. Augenh., **62**:353, 1919.
3. Terrien, F., and Veil, P.: Bull. Soc. franç. ophtal., **42**:349, 1929.
4. Kraupa, E.: Arch. f. Genhk., **109**:416, 1936.
5. Kronfeld, P. C.: Arch. Ophth., **32**:447, 1944.
6. Givner, I.: Am. J. Ophth., **32**:1131, 1949.
7. Kornzweig, A. L.: Am. J. Ophth., **36**:123 (Jan.) 1953.
8. Rychener, R. O.: Am. J. Ophth., **37**:267 (Feb.) 1954.
9. Billet, E.: Am. J. Ophth., **35**:214 (Feb.) 1952.
10. Theodore, F. H.: Brit. J. Ophth., **36**:207 (Apr.) 1952.
11. Vouters, J.: Bull. Soc. ophtal. France, 1951, p. 695.
12. Israel, E. B.: African M. J., **26**:809, 1952.
13. Zewi, M.: Ann. Chir. & Gynec. Fenniae, **43**:539 (Suppl. 5) 1954.
14. Mattsson von Ragnar: Acta. Ophth., **32**:523, 1954.
15. Posner, A., and Schlossman A.: Tr. Am. Acad. Ophth., **57**:531, 1953.
16. Grant, M. W.: Arch. Ophth., **46**:113, 1951.
17. Burton, E. W.: Southern M. J., **50**:257-258, 1957.
18. Rud, E.: Acta Ophth., **35**:406-410, 1957.
19. Posner, A., and Schlossman, A.: J.A.M.A., **139**:82 (Jan.) 1949.
20. Posner, A.: EENT Monthly, **31**:41, 1952.
21. ———: Am. J. Ophth., **40**:576 (Oct.) 1954.
22. ———: New York State J. Med., **56**:199, 1956.

VITAMIN-A INTOXICATION

Charles A. Turtz, M.D.

and

Arnold I. Turtz, M.D

New York

The use of vitamin A in the treatment of acne has long been established. An occasional case of intoxication has been reported in the literature.*

Case report

A 17-year-old boy consulted us in January, 1958, and gave a history of headaches, blurred vision, and

* Oliver, T. K., Jr., and Havener, W. H.: Eye manifestations of chronic vitamin-A intoxication. A.M.A. Arch. Ophth. **60**:19-22 (July) 1958.

occasional attacks of diplopia. This was accompanied by general malaise and pains in the joints. The eye symptoms had been present one week prior to his visit. He was tall, and thin and appeared distraught. His visual acuity was 20/50, R.E.; 25/30, L.E. Lids were negative and hemic content was good. There was no muscle imbalance. Slitlamp microscopy revealed no pathologic condition in the cornea or lenses. Examination of the fundi revealed small discrete superficial hemorrhages throughout the retina of both eyes but more marked in the right. The appearance of the vascular tree was normal. There was early edema of the left disc.

On further questioning we were told he had been taking 200,000 units of vitamin A daily for 18 months for acne.

Vitamin A was discontinued. Symptoms gradually disappeared and within 10 days vision returned to 20/25 in each eye, the edema of the left disc subsided, and only an occasional discrete hemorrhage toward the periphery remained.

Comment

In addition to the symptoms and clinical signs in our case, vitamin-A intoxication can produce exophthalmos, increased intracranial pressure with chocked discs, loss of hair, enlarged spleen and liver, skin rash with desquamation and cutaneous pigmentation.

525 Park Avenue.

CROSS-ACTION NEEDLE HOLDER*

Robert E. Bartlett, M.D.
Los Angeles, California

The cross-action lens capsule forceps has become the instrument of choice in its line. It requires only a light grasp by the operator during the delicate maneuver of delivering the lens, and the jaws of the instrument can easily be opened without shifting the position of the fingers. The same reasons prompted me to design a cross-action needle holder.

The cross-action needle holder has become practical only since the advent of the newer type sharper ophthalmic needles. Too great a spring action would be required to grasp a dull needle firmly and push it through the cornea. This in turn would require too much force by the operator to open the jaws to release the needle.

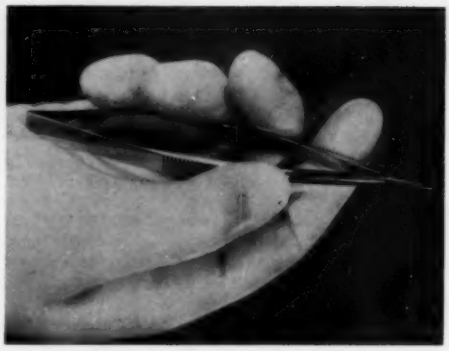


Fig. 1 (Bartlett). Design of cross-action needle holder.

The strength of the spring of the present instrument is delicately balanced to hold the needle without rotation or sliding during corneal or scleral surgery. Yet it is not so strong that the needle cannot be released without undue effort. Figures 1 and 2 show its general design. It is slightly larger than the Paton and slightly smaller than the Castroviejo needle holder, measuring 12.5 cm. in length. Its design permits it to be held in

Fig. 2 (Bartlett). This view illustrates a way of holding the instrument which is particularly convenient in certain circumstances.

* From the Department of Ophthalmology, Wadsworth Hospital, Veterans Administration Center, and the Department of Ophthalmology, University of California Medical Center at Los Angeles. This instrument is available at Storz Instrument Company, Saint Louis, Missouri.

two ways (figs. 1 and 2). The method illustrated in Figure 2 is particularly applicable in certain circumstances. When inserting scleral sutures posterior to the limbus, the instrument is held like a pencil which directs the jaws conveniently downward. This allows the surgeon to direct the instrument posteriorly without bending the wrist into an awkward position.

1001 Gayley Avenue.

RECESSION FORCEPS*

DuPont Guerry, III, M.D.
Richmond, Virginia

For the past several years I have used a recession forceps of somewhat unique design. The forceps has a grip for both the middle and index finger and a push button for thumb action. The jaws, in crenelated form, have four notches on each side to facilitate the placing of sutures. There are five projections from the under side of the upper jaw that fit into corresponding female openings in the upper part of the lower jaw, thereby insuring a firm grasp of the muscle tendon. An expanding spring closes the jaws and if one desires absolute security, they may be locked in any position by means of a knurled set screw. When the set screw is in the unlocked position, the jaws are easily opened by pressure on the thumb button.

I have found that this instrument has greatly facilitated horizontal recession surgery, both as to ease and speed of application and removal. The instrument is easily dismantled for cleaning and holds up extraordinarily well in service. The original forceps, now over three years old, is still in service. The forceps come in two sizes, one for adults and one for children, the only difference being that the blade in the children's forceps is two mm. shorter than that in the adult instrument.

* From the Department of Ophthalmology, Medical College of Virginia. The instrument is made by the Matalene Surgical Instrument Company, Inc., successors to E. B. Meyrowitz.

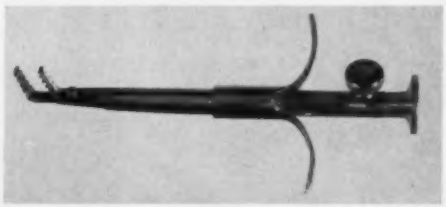


Fig. 1 (Guerry). Recession forceps with open jaws.

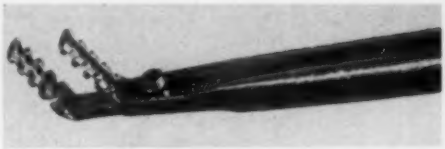


Fig. 2 (Guerry). Magnified view of jaws, showing notches for placing sutures.

LENS-IRIS FORCEPS*

FOR CATARACT EXTRACTION

A. Benedict Rizzuti, M.D.
Brooklyn, New York

With the advent of alpha chymotrypsin, lens removal can now be accomplished with greater facility. The enzymatic zonulolysis that results has altered certain standard techniques of cataract extraction that were routinely employed by a large number of ophthalmic surgeons. This is particularly true of the tumbling technique.

Alpha chymotrypsin may very well tend to increase the popularity of the sliding technique from above because it provides greater visibility. It may also make more popular round pupil cataract extraction.

The surgical procedure can be further simplified with the use of proper iris retraction. To accomplish this, I previously suggested and described† a lens forceps with a

* From the Brooklyn Eye and Ear Hospital.

† Rizzuti, A. B.: A lens forceps with iris retractor: For round pupil cataract operation. Am. J. Ophth. **45**:277 (Feb.) 1958.

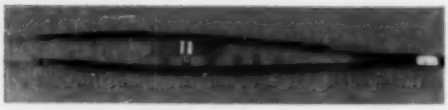


Fig. 1 (Rizzuti). Lens-iris forceps for cataract extraction.

retractor lip which has since been modified and simplified‡ (figs. 1 and 2).

A Verhoeff lens forceps is now used in which one small circular fenestrated blade remains unchanged. Its opposite blade is solid, to which a short protruding slightly concave ledge has been molded to its most distal end. The ledge or lip can be gently slipped under the iris body through the pupillary area to effect proper iris retraction and facilitate the grasping of the superior lens pole when the two blades are approximated. Slight limbal pressure below is desirable to tilt the upper pole of the lens forward.

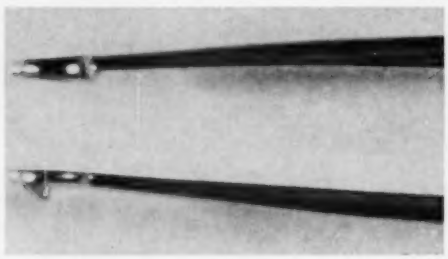


Fig. 2 (Rizzuti). Showing shelf for iris retraction.

The ledge measures 1.25 mm. in height and hence is shallow enough so as not to stretch the iris unduly. The drawn-up iris slips off with comparative ease when an attempt is made to grasp the lens at its superior pole.

This improved model has been a welcomed adjunct in performing round-pupil intracapsular extractions by the "sliding technique" from above particularly in cases where the pupil has contracted as a result of excessive lavage of the anterior chamber or other causes.

160 Henry Street (2).

‡ This instrument may be obtained from the Storz Instrument Company, 4570 Audubon Avenue, Saint Louis 10, Missouri.

A MODIFIED KERATOME*

WALTER L. BAYARD, M.D.
Park Ridge, Illinois

The keratome has undergone slight modification since its inception. In my hands it presented several limitations in initiating the section of the cornea in a cataract operation: (1) poor visibility of the wound site and preplaced corneoscleral sutures; (2) lack of visibility and lack of ease in depressing the heel of the keratome after the initial penetration into the anterior chamber.

The modification presented here (fig. 1), in my hands at least, does away with the preceding objections. It offers a perfect

Fig. 1 (Bayard). A modified keratome.

view of the wound site and sutures, and by merely rotating the handle in the fingers, the heel is depressed and the blade enters further into the chamber.

The modified keratome may be used for either right or left eyes because the angle of handle allows one to "go over the nose" in left eyes. A left-handed model is available for surgeons who use the keratome in the left hand.

* From the Illinois Eye and Ear Infirmary of the University of Illinois College of Medicine. The instrument is available at V. Mueller and Company.

OPHTHALMIC RESEARCH

EDITED BY FRANK W. NEWELL, M.D.
950 East 59th Street, Chicago 37, Illinois

Abstracts of papers presented at the meeting of the Midwest Section of the Association for Research in Ophthalmology, Inc., Indianapolis, Indiana, April 23 and 24, 1960.

T. F. SCHLAEGEL, JR., M.D., *Indianapolis, Indiana*
Section Secretary

Glaucoma family study. Allan E. Kolker, M.D., F. Dale Roth, M.D., Bernard Becker, M.D., Department of Ophthalmology and the Oscar Johnson Institute, Washington University School of Medicine, Saint Louis, Missouri.

A group of 110 close relatives of patients with chronic simple glaucoma were given complete eye examinations. The results of test procedures in this group were compared with the results of similar procedures in the normal population. The prevalence of an intraocular pressure of 30 mm. Hg or higher was 5.5 percent for the entire study group and 9.7 percent for the relatives 40 years of age and older. An elevated intraocular pressure after water to over 24 mm. Hg (that is, higher than three standard deviations from the normal mean), was found in 9.1 percent of the total group and in 16.1 percent of the group 40 years of age and older. Of the study population 16.4 percent had facilities of outflow which were less than 0.13 (more than three standard deviations from the normal mean). This degree of impairment occurred in 22.5 percent over the age of 40 years.

The average values for the entire group for pressure and outflow facility were significantly different from those for the normal population, with the intraocular pressure being higher and the facility of outflow lower. Forty percent of the family population studied had Po/C ratios of 100 or more.

Histologic and clinical studies of the glaucoma secondary to retained intraocular iron foreign body. Tsuyoshi Yamashita, M.D., Bernard Becker, M.D., and Glen Johnston, M.D., Department of Ophthalmology, Washington University School of Medicine, Saint Louis, Missouri.

The relation of iron toxicity to chronic open-angle glaucoma was studied. Six out of 15 human eyes enucleated with retained intraocular iron foreign bodies were found to have open-angle glaucoma. Deposition of iron in the filtration angle and degeneration and endothelial proliferation of the trabeculae were demonstrated histologically in these eyes.

Saccharated iron oxide was found to stain intertrabecular acid mucopolysaccharide in both living animal and enucleated human eyes. Acute glaucoma was produced in rabbits with anterior chamber injection of saccharated iron oxide and histological changes similar to those in the clinical eyes were present one month to two years later.

It is felt that iron may effect the intertrabecular acid mucopolysaccharide and endothelial cells in such a manner as to produce a form of chronic open-angle glaucoma.

The localization of Diamox-S-35 in the rabbit eye, Seymour B. Goren, M.D., and Frank W. Newell, M.D., Department of Surgery (Ophthalmology), The University of Chicago.

The localization and metabolism of Diamox in the rabbit eye have been studied by means of S-35 incorporated acetazolamide and autoradiographic and chromatographic techniques. Male albino rabbits were given a single dose of one millicurie per kilogram of body weight of Diamox-S-35 into the marginal vein of the ear. The specific activity of the compound was 82 mc. per mg. Two hours later, 20 mg. of heparin was administered intravenously and the animal was anesthetized with pentobarbital sodium. The chest was then opened, the aorta cannulated through the left ventricle, and the rabbit perfused with 2,000 cc. of human plasma containing 0.375 mg. per cc. of nonradioactive Diamox. With this technique, the eyes were perfused until free of blood. The eyes were processed with a freeze-dry technique and autoradiographs were made.

The ciliary processes, iris, and inner layers of the retina were found to have the highest concentrations of Diamox. The next greatest concentrations on the autoradiograms were the corneal endothelium and Descemet's membrane. The sclera contained moderate amounts of Diamox, less than the above-mentioned heavily impregnated tissues, but more than the corneal stroma and epithelium. Very little Diamox was found in the lens and only with overexposure of the plates could an autoradiographic image of the lens be seen. More Diamox concentrated on the anterior surface of the lens than on the posterior surface with the transition from darker to lighter areas taking place in the vicinity of the equator. Minimal quantities of Diamox were seen in the choroid. The level here was difficult to determine because of the marked shrinkage of the posterior uveal tract during freezing and dehydration.

Chromatograms of the extracts from the whole homogenized eye revealed no difference from the pure control Diamox S-35; that is, all had only one band of the same magnitude, whether or not

the eye had been perfused. Therefore, it may be assumed that Diamox in the eye is in an unaltered state.

It is felt that the localization of Diamox in the rabbit eye is partially dependent upon a preferential uptake of specific tissues with a superimposed Diamox-binding capacity of those tissues.

Experimental tonography: The effect of anticholinesterases. Marguerite A. Constant, Ph.D., and Bernard Becker, M.D., Washington University Medical School, Saint Louis, Missouri.

DFP has been shown by others (and confirmed in the present studies) to cause severe miosis and a rise in intraocular pressure in the rabbit. A newer, water-soluble, potent anticholinesterase (echothiophate) has similarly been observed in the present studies to cause severe miosis and a marked rise in intraocular pressure in this species. An approximately maximal effect is caused by one drop of 0.1 percent topically. A higher concentration (0.25 percent) increased slightly the responsiveness of the animals. A lower concentration (0.05 percent) was equally effective in some but the number of maximally responding animals was decreased. Demecarium bromide (BC-48), 0.25 percent or 1.0 percent, caused equally severe miosis but inconsistent and insignificant intraocular pressure change.

The pressure effect of echothiophate was inhibited for several days following its administration or that of demecarium bromide. It was generally prevented by topical pretreatment with vasopressin and reversed by posttreatment with acetazolamide or vasopressin. The pressure rise did not occur in eyes with patent iridectomies. Using this test system, a newer antidote for "irreversible anticholinesterases," 1,1'-trimethylenebis (4-formylpyridinium bromide) dioxime (TMB-4), appeared to be more effective than pyridine-2-aldoxime methiodide (2-PAM). TMB-4 acted more rapidly at lower dose levels and appeared to be more stable in solution.

Ocular effects of the oxygen analogue of Co-Ral. Maurice Kadin, M.D., The University of Chicago.

The oxygen analogue of Co-Ral (Bayer), (diethyl-0-3-chlor-4-methyl-7-coumarinyl phosphorothionate), a commercial insecticide, is a potent miotic and anticholinesterase agent. It inhibits brain cholinesterase and thus probably penetrates the blood-brain barrier. It is only slightly water soluble but is soluble in peanut oil.

The oxygen analogue was instilled into the right eye of albino rabbits and dogs in 0.25 percent concentration in peanut oil three times a day for periods up to one month. It was used in the treatment of human glaucoma for periods up to one year.

Manometric and colorimetric studies of cholinesterase activity indicated no activity in primary aqueous humor or normal rabbits or following treatment with Co-Ral or the oxygen analogue.

Following ocular instillation of the oxygen analogue inhibition of cholinesterase activity was found in all tissues studied. The following percent of normal cholinesterase was found: iris, ciliary body, 15 percent; retina, 50 percent; brain (cortex plus white matter), 25 percent; salivary gland, 55 percent; ileum, 36 percent; blood serum, 51 percent; erythrocytes, 53 percent. Protein increased in the aqueous humor to maximum levels of 750 mg. percent.

Studies of blood serum in the dog showed inhibition to 40 percent of normal activity after 28 days treatment. In the rabbit there was complete inhibition of pseudocholinesterase. In humans treated up to one year with coralox, complete inhibition of the pseudocholinesterase of serum was found. There was no inhibition in erythrocyte cholinesterase in man.

Study of the distribution of oil emulsions of phenol red and fluorescein following instillation into the rabbit eye indicated easy passage of the emulsion to the lungs through the lacrimal system. Systemic effects arose presumably from pulmonary absorption of the anticholinesterase.

Observations on effects of cholinergic and adrenergic drugs on the zonule and ligament of Wiegert in rabbit eyes. Maurice Kadin, M.D., The University of Chicago.

In albino rabbits treated with coralox, the zonules of the lens ruptured readily, so that the lens delivered easily. Albino rabbits (2.0-3.0 kg.) anesthetized with intravenous Nembutal were used. The following drugs were studied: coralox 0.25 percent, carbaminoylcholine 1.5 percent, phospholine iodide 0.25 percent, diisopropyl fluorophosphate 0.1 percent, demecarium bromide 0.25 percent, and 1 : 1000 epinephrine.

The lens was grasped with a Bell erisophake. When compounds were instilled locally a cataract extraction was simulated. In other studies the cornea was removed, meridional sections made in the iris sphincter, and the erisophake attached by a Hoffman screw compressor to a pulley system connected to a pan having an effective weight of 24 gm.

The zonule of normal rabbit eyes sustained the pull of this weight for periods up to two and one-half hours, with a minimum period of over one hour. The ligament of Wieger was found to remain firmly attached and intact.

Following instillation of phospholine two times a day and coralox as eye drops three times a day for 14 days, it was possible to remove the lens without vitreous in seven of eight experiments. Demecarium did not produce this effect after 21 days instillation. Instillation of aqueous soluble compounds into the anterior chamber did not decrease the time period for zonule rupture.

Injection of 0.1 ml. of water soluble compounds into the anterior chamber or vitreous humor caused marked congestion of iris and marked

miosis. The weighted pulley erisophake caused removal of the lens in one to five minutes. Epinephrine dilated the pupil and produced the same effect in seven to 10 minutes but failed in two of six eyes. The mechanism of action is now known.

A study of vitamin A: Deficiency in the cat with special reference to the central nervous system and the eye. R. S. Kirkegaard, M.D., Department of Ophthalmology, University of Iowa, Iowa City.

Since the retina rests in the initial position of direction in the complex chain of neural excitation that ends in the sensation of vision, the retinal nervous excitation reflected by the electroretinogram projects certain of its qualities to the remainder of the neuro-optic pathways. By comparing the "input" at the retinal level with the "output" response within the brain, it is felt that a better understanding of the relationship will be obtained with and without sufficient vitamin A.

The following program has been established to evaluate the effect of vitamin-A deficiency in cats. It is thought that early functional changes can be detected by utilizing electroretinography and by electrodes permanently implanted in the brain. Later changes in cells and fibers will be evaluated histologically, including the Marchi stain to demonstrate degenerating myelin. The tissues to be evaluated are the eye, brain (brain stem especially), certain cranial nerves, and liver. In addition, liver and blood samples will be assayed for vitamin A and beta-carotene levels at several stages during the depletion.

The intracranial electrodes are placed stereotaxically in the optic chiasm, lateral geniculate body, superior colliculus and occipital cortex. These are held firmly in place with dental acrylic which is anchored to bone. The stimuli consists of stroboscopic flashes and microvolt electric discharges via the electrode in the optic chiasm.

The evoked responses are carried to the preamplifier system and then to a dual beam cathode ray oscilloscope, at which point they are recorded with either a polaroid camera or a Grass movie camera. To reduce movement artefacts and to standardize the recording conditions, the animal receives Bulbocapnine and is suspended in a light-proof cage at a specific distance from the light source.

Both pupils are dilated maximally with Neosynephrine and the lids held apart with retractors. The intracranial electrodes are attached to a multilead transitor jack which runs to a selector panel before entering the preamplifiers. Thus, the ERG and any one of the other responses can be recorded simultaneously.

Five cats have been maintained on the diet for three months to date and have been subjected to many recording periods as described above. Each has had one liver sample and two blood samples assayed for vitamin A and beta-carotene. Preliminary impressions indicate that the technique described above it a satisfactory one for evaluating the neuro-ophthalmic effects of vitamin-A deficiency in the cat.

Clinical and experimental aspects of retinitis proliferans. Tsuyoshi Yamashita, M.D., and Paul A. Cibis, M.D., Department of Ophthalmolgy, Washington University, Saint Louis, Missouri.

Ophthalmoscopic and histopathologic manifestations of retinitis proliferans have been observed in 10 out of 17 rabbit eyes subjected to intravitreal injections of 0.1 cc. of autogenous blood, and in 14 out of 23 rabbit eyes treated with intravitreal injections of 0.1 cc. of a solution of saccharated iron oxide (0.2 mg. elementary iron). The various forms of fibrous and/or fibrovascular tissue proliferation developed in periods of two weeks to two years in each group. They originated either from prepapillary mesenchymal tissue of Kuhnt or from preretinal or perivascular fibroblastic elements. In each instance they were independent from the more or less distinct fibrous ingrowth occurring at the site of injection. The opposite eyes of the animals served as controls. They were subjected to intravitreal injections of equal amounts of physiologic saline solutions at/or somewhat anterior to the equator. The fibrous reactions in the control cases were less marked and limited to the site of injection.

The clinical aspects of this study concerned the description and demonstration of proliferative retinal changes in enucleated human eyes with (1) iron foreign bodies retained in the eye over a period of nine months and more, or with (2) diabetic retinopathy. In the former group, eight out of 15, and in the latter 11 out of 13 eyes revealed fibrovascular reactions associated with demonstrable cytoplasmic and/or extracellular siderosis or hemosiderosis.

The mode of siderogenous fibroblastic excitation is unknown. Several possible hypothetical mechanisms are discussed.

Photic driving in amblyopia ex anopsia. James E. Miller, M.D., Laverne C. Johnson, Ph.D., George A. Ulett, Ph.D., and Jack Hartstein, M.D., Departments of Ophthalmology and Psychiatry, Washington University School of Medicine, Saint Louis, Missouri.

Photic driving has been used as a technique to evaluate the response of the occipital cortex to light in 33 amblyopic and 16 nonamblyopic patients.

No difference was noted between the amblyopic eye and the nonaffected eye. The maximum driving was obtained in the eight to 12 flashes per second (alpha) range in each eye. Reducing the illumination did not alter the monocular response.

Binocular driving demonstrated an alteration between the amblyopic subjects and the control subjects. Patients with amblyopia had significantly less photic driving in the range of eight to 18 flashes per second, and greater in the three to seven area. Nonamblyopic subjects responded

greatest in the eight to 13 flashes per second range with both eyes open. It was felt that the above findings are an indication of suppression that exists only under a binocular situation.

A blind clinical comparison of the routine EEG's did not demonstrate any statistical difference between the two groups.

Permanent fractionation of the electroretinogram in glutamate poisoning. Albert M. Potts, M.D., Robert W. Modrell, M.S., and Cecil Kingsbury, The University of Chicago Eye Research Laboratory, and Laboratory for Research in Ophthalmology, Western Reserve University, Cleveland, Ohio.

Following the work of Lucas and Newhouse, we were able to prepare mice whose retinas consisted essentially of receptor cells by the use of sodium-L-glutamate injections immediately after birth. These animals showed what appeared to be histologically an intact set of receptor cells and all other retinal cells confined to a double layer of nuclei. Animals with this type of histological finding showed an electroretinogram consisting of an a-wave only. Wherever inadequate dosage of glutamate allowed a complete electroretinogram to be manifest, histology showed a definable layer of bipolar cells. Thus, there is a direct connection between b-wave and the presence of bipolar cells and it seems a good first assumption to attribute the origin of the b-wave to this particular cell group.

In reviewing the problem of how sodium-L-glutamate, a normal body constituent, can have such a specific toxic function, the high levels of glutamine synthetase and glutaminase in the developing eye were taken into consideration. It seemed likely that the effect was best explained on the basis of repression of enzyme formation in a growing animal by a feedback mechanism, activated by one of the reaction products.

Investigation is continuing both on the electrophysiology and the biochemistry of this phenomenon.

Effect of two hallucinogens on retinal function in man. Alex E. Krill, M.D., Anna Wieland, and Adrian M. Ostfeld, M.D., College of Medicine (Chicago). Departments of Ophthalmology and Preventative Medicine, University of Illinois, Chicago.

D-lysergic acid diethylamide (LSD-25) and n-ethyl-3-piperdyl benzilate hydrochloride (JB 318) induce visual hallucinations in man. However, it has never been demonstrated where these drugs act to induce this phenomenon. This study was undertaken to evaluate the effects of these drugs on retinal function in man and to relate possible retinal effects to hallucinations. Nineteen medical students with normal eyes participated in 40 experiments. Retinal function was tested with: (1) dark adaptation by means of the Goldmann-Weekers adaptometer, (2) the ERG by means of Burian-Allen contact lens electrodes, the Grass encephelograph, and photic stimulator, and (3) color vision by Hardy-Rand-Rittler plates. Testing was done with the pupils dilated and with a standard preadaptation of 2,400 lux. A range of doses of both drugs was employed. To determine if retinal effects were dose dependent, five subjects were given low nonhallucinogenic doses of both drugs as well as larger hallucinogenic doses. As an additional control, analogs of both drugs were also used. Significant changes in retinal function occurred only in those subjects that hallucinated. These changes consisted of (1) an elevation of the entire rod curve during dark adaptation, (2) a delay in the rod-cone break, (3) an increase in the scotopic b-wave amplitude at all intensities, and (4) a frequent, though inconsistent, increase of the a-wave at all intensities. No effect on color vision was noted. The changes in the dark-adaptation curve were compatible with a mild impairment of rod function. The changes in the ERG components were postulated to relate to a toxic or hypoxic effect of the hallucinogen on the retina. No changes were noted in control studies or in postdrug studies of the analogs and low doses of the hallucinogen. These findings indicate that the hallucinogenic effect of psychotomimetic drugs are related to concomitant changes in retinal function.

Subjective evaluation of ocular proprioception monitored with the use of electro-oculograms. Robert D. Reinecke, M.D., and Charles M. Poser, M.D., University of Kansas Medical Center, Kansas City, Kansas.

The use of electro-oculograms makes possible the monitoring of eye movements in a completely darkened room. This principle was utilized to study the amount of knowledgable eye movements in a completely darkened, as compared to a well-illuminated room. The effect of topical anesthetic on the conjunctiva and cornea was also studied under the conditions just mentioned. It was found that the only knowledgable eye movements which could be elicited were actually awarenesses of retinal image changes (retinoception). The subjects had no knowledge of eye movements in a complete darkness. Voluntary eye movements in the dark were characterized by the patient signaling before his eyes moved by approximately $\frac{1}{20}$ of a second. No change in response was noted after instillation of topical anesthetic to the conjunctiva. Since the afferent impulses from extraocular muscles do not reach conscious levels, these impulses do not fit the present definition of "proprioception."

A technique for extraocular electromyography in chronic animals. James A. Stuart, M.D., Department of Ophthalmology, University of Iowa, Iowa City.

This paper presents an investigative technique for obtaining repetitive electromyographic recordings from the extraocular muscles of the cat. The procedure has the advantage that the animal is living, not narcotized, and not anesthetized and

thus approaches a normal physiologic, in vivo preparation. Electromyograms for comparison may then be recorded from the same animal before and after introducing additional factors such as neurosurgical procedures or drugs.

The electrodes consist of fine (38 gauge) enamel insulated, nichrome wires which are paired and inserted into the muscle belly and tendon respectively. The wires are looped through the muscle to provide permanent fixation. It has been found that the electrodes are still in position when the animal was killed as much as one and one-half months later. The surgical approach is through the frontal sinus with removal of the orbital roof. Outside the muscle the electrodes are presoldered to common, rubber insulated electrical wires which pass upward out of the orbit and then beneath the scalp to emerge through the skin in the posterior cervical region. The free ends of these wires may then be quickly and repeatedly connected to oscillograph leads, at any time following the operative procedure, without further manipulation of the animal. Electromyograms recorded with this technique have demonstrated the typical resting interference pattern and recruitment with eye movement.

Thermodynamics of the intraocular and extraocular muscles. Julia T. Apter, M.D., Departments of Ophthalmology and Physiology, Northwestern University, Chicago.

Temperature changes alter the tension of smooth and striated unstimulated muscle. By in vitro study of cat and dog orbital muscles freshly prepared and protected from extremes of stretch and oxygen deprivation, the temperature-tension correlation was found to suggest an equilibrium between two forms of a contractile substance. The correlation was a negative sigmoid curve which fit the form

$$f = \frac{f_{max}e^{-B/T} + f_{min}}{1 + e^{-B/T}}$$

where f is the force at absolute temperature T; f_{max} is the highest force induced by temperature (at 5°C.) and f_{min} is the lowest force (at 40°C.). B is a function of the slope of data rectified by a log-reciprocal transform and of the temperature at which the log term is zero. A mecholyl stimulated iris sphincter responds to temperature according to this same equation; f_{min} not changing at all while f_{max} changes more than all other forces at intermediate temperatures. The muscle acts as though the contractile element is incapable of responding to mecholyl at 40°C. We call this element A_R (relaxed). At lower temperatures some of A_R has been altered to a form which can respond to mecholyl. This form we call A_C (contracted). Since thermal changes alone can convert A_R to A_C, reversibly, the contractile substance acts as though there is an equilibrium between these two forms. Since the force (f) at temperature (T) is a measure of the amount of A_R and A_C persent, the equilibrium constant for the reaction can be expressed entirely in measured forces. Therefore, from the van't Hoff equation the heat of reaction can be calculated. Also, from the Gibbs-Helmholtz equation the entropy changes can be calculated. These calculations indicate that the transformation from relaxed to contracted form is an exothermic reaction consistent with active heat production measurements or muscle. What is more, the entropy change suggests that A_R is more disorganized than A_C, a possibility consistent with X-ray diffraction and electron microscopic studies of the contractile proteins in muscle.

Responses and distribution of muscle in the human eye. Julia T. Apter, M.D., Departments of Ophthalmology and Physiology, Northwestern University, Chicago.

The intraocular muscles of the human eye were investigated with a method which successfully plotted the distribution of muscle in the iris of cats and dogs. (Am. J. Ophth., 1959; Am. J. Physiol., 1960). With this method, each muscle (sphincter, "dilator," and ciliary muscles) was isolated. In a suitable artifical medium the tensions developed in response to electric current, mecholyl, adrenalin and temperature changes were measured with a strain gauge suitable for these small muscles. The sphincter muscle relaxed to adrenalin but contracted to other stimuli, more strongly in the circumferential than in the radial direction. The ciliary muscles contracted equally to all stimuli and in both radial and circumferential directions. The "dilator pupillae" did not respond at all. Temperature changes produced in the sphincter and ciliary muscles the responses usually found in smooth muscle while the "dilator" responded like rubber or elastic tissue. We must conclude that the structures in the eye which are histologically identifiable as smooth muscle also act like smooth muscle. On the other hand, the dilator behaves like an elastic polymer, not like muscle and also does not resemble muscle in appearance.

A study of the distribution of actual muscle in the eyes of cats, dogs, and humans reveals why the dilator was mistakenly called a muscle. The experimenters who found radical contractility in cats and dogs were not aware that the ciliary muscles extend into the iris substance in these species. The radial fibers in these muscles, not in the spurious "dilator" were the source of the radial contractility they observed.

Phagocytic elements in the eye. Johannes Rohen, M.D., Department of Ophthalmology, Washington University, Saint Louis, Missouri.

Experimental studies were carried out on phagocytosis in rabbit, dog and monkey eyes. Methods: Dextran, cellulose or pigment-solutions were injected into the anterior chamber or the vitreous. In short-term experiments the injected material was found chiefly in histiocytes, leukocytes and monocytes of the mesodermal tissue of the ciliary processes, iris and optic nerve. In long-term ex-

periments, extending over a period of several weeks, the injected substances were seen in the endothelial cells of the trabecular meshwork, the endothelium on the surface of the iris and by cells located between the zonule fibers. The findings in rabbit eyes differed from those in other species studied in so far as the injected material was phagocytosed chiefly by histiogenic elements of the optic nerve.

The effect of endothelial curettement on corneal wound healing: Experimental study. James E. McDonald, M.D., Department of Ophthalmology, University of Illinois College of Medicine, Chicago.

This work concerns itself with the effect of endothelial curettement on the course of corneal wound healing in the rabbit eye. We have attempted to determine these effects on each component of corneal wound healing, that is the effect on the stromal, fibrin, epithelial and fibroblastic phases. In Experiment I, 17 rabbits had a 5.0-mm. central penetrating corneal incision of a Saemisch type made on each eye. Immediately after the incision the endothelium of the right eyes was gently curetted through this central incision. Only the wound edges of the left eye were traumatized to correspond to the trauma incurred during curettement of the other eye. No sutures or medications were used after the incision.

Both eyes of seven rabbits were similarly incised but only the inferior portion of the right cornea and the superior portion of the left cornea were curetted. These were followed up to a period of one month by slitlamp examination, external photographs and histologic sections. Counts of epithelial cells, eosinophiles and fibroblasts were made on four sections of each eye at one day, three days and four days postoperative.

Conclusions: Endothelial curettement under the conditions of the experiment (1) causes marked stromal edema which does not cause abutment of the wound edges and may even cause their increased separation; *(2)* causes dense fibrinous adhesions of the iris and lens to the curetted cornea resulting in a flat chamber under the curettement, permanent anterior synechias, secondary glaucoma and seems to interfere with the solidarity of the fibrin plug; (3) causes epithelial edema but does not interfere with its migration over the wound; (4) does not retard and possibly increases fibroblastic activity in the wounded cornea.

Influence of fixatives and autolysis on the structures of the crystalline lens. Ralph G. Janes, Ph.D., and Richard D. Richards, M.D., Departments of Anatomy and Ophthalmology, State University of Iowa, Iowa City.

The histologic structure of the crystalline lenses of rats may be altered to a certain degree by the fixative used. Following enucleation of the eye small amounts of 10-percent formol, Carnoy's or Davidson's fluids were injected into the vitreous chamber, and the eye was immersed in the same fixative for 24 hours. Davidson's fluid appeared to cause the fewest artifacts in the lenses. In the study of autolytic changes, lenses were fixed at 0 hours up to 12 hours following death. The first postmortem alterations were seen at one-half hour, when small vacuoles were noted near the surface nuclei at the equator of the lens. At one hour there was some swelling of the lamellae and displacement of fibers in deeper areas of the cortex with a collection of homogeneous fluid. At three hours there were small vacuoles in some of the cortical fibers and displacement of nuclei was noted at the equator. The vacuoles increased in number and size by eight hours. By 12 hours the nuclei were showing degenerative changes and in many instances it was difficult to find any normal lens tissue. If glucose was given intraperitoneally in acute or chronic experiments before the animals were killed, the autolysis seemed to be speeded up. Many of the autolytic changes described appear to be similar to the early lens changes noted in animals with diabetes.

Comparative enzymology of lenticular peptidases. Renuka Banerjee, M.D., David Shoch, Ph.D., M.D., and E. Albert Zeller, M.D., Departments of Biochemistry and Ophthalmology, Northwestern University Medical School, Chicago.

In previous papers (Am. J. Ophth., **44**, II, 281, Federation Proc., **18**, 358) an enzyme has been described which catalyzes the hydrolysis of L-phenylalanine ethyl ester (PAEE). In addition to PAEE beef lens homogenates a number of other L-amino acid esters, but not D-amino acid derivatives. The amides of L-leucine and L-phenylalanine were more rapidly hydrolyzed than the corresponding esters. Several cations such as Co^{++}, Mn^{++}, Fe^{++}, Ni^{++}, Mg^{++}, and Cd^{++} activate the enzyme and chelating agents such as EDTA inhibit it. Fe^{+++} is without effect while the same cation in presence of ascorbic acid activated strongly. It seems possible that ascorbic acid which in the lens is present in large quantities and which is kept there in reduced form regulates the activity of this peptidase through its influence on the state of oxidation of cations.

Similar studies were carried out with rabbit lens homogenates. The substrate pattern for this material is essentially the same. However, quantitative differences appeared, particularly for N-methylphenylalanine ethylester and for the two amides mentioned above. Furthermore, the rabbit lens enzyme seemed to be little influenced by cations and EDTA. One exception was found in the hydrolysis of the two amides which were activated by Co^{++}. In the few experiments carried out with the enzyme present in normal human lenses it displayed properties similar to the rabbit peptidase.

Rabbit and beef lens peptidases, therefore, are related, but not identical enzymes. They seem to belong to a group of closely related—homologous—enzymes.

Electron microscopic study of early changes induced by fast neutron irradiation of rabbit lens and ciliary body. T. Tokunaga, M.D., E. F. Riley, Ph.D., and R. D. Richards, M.D., Department of Ophthalmology and Radiation Research Laboratory, State University of Iowa, Iowa City.

It has been shown that histologic changes occur in an irradiated lens prior to the clinical observation of cataractous change. In an attempt to clarify the mechanism of formation of radiation cataract and the difference between fast neutron injury and roentgen-ray injury to the lens, the epithelial cells and the young lens fibers of irradiated lens were investigated by means of electron microscopy during this latent period of experimental radiation cataract.

Since some investigators believe that the primary site of radiation injury is not the lens epithelium but the ciliary epithelium, the authors observed the ciliary body and compared these findings with those of the lens.

Young albino rabbits weighing 650 to 1,300 gm. were used. Fast neutron radiation was generated by a 60-inch cyclotron (Argonne National Laboratory). Doses of about 400 rad on the right eye and 500 on the left eye were employed. Because these neutrons have been shown to be about four times as cataractogenic as 250 kvp X rays, these doses were cataractogenically equivalent to exposures of 1,600 and 2,000 rad of x-radiation.

The rabbits were killed by injection of air into the vein of the ear 24 hours (three rabbits), 48 hours (three rabbits), and four days (two rabbits) after irradiation with fast neutrons. Ultrathin sections of the lens and the ciliary body were made by standard methods and examined by means of the electron microscope.

All rabbits were observed by means of the ophthalmoscope and slitlamp every 24 hours.

The results of this study were as follows:

1. Many vacuoles occurred in some epithelial cells beginning 24 hours after irradiation. Some of these vacuoles appeared to be from mitochondria because the membrane of the vacuoles was triple layered and occasionally remains of cristae mitochondriales were seen. Other vacuoles appeared to be from endoplasmic reticulum since Palade's granules were often seen on the surface. The source of some vacuoles was unknown. The largest vacuole was 10 $\mu \times 10\ \mu$ in size. In other epithelial cells, only a few mitochondria were moderately swollen and cristae mitochondriales of these were displaced or distorted. There was little change seen in Golgi apparatus. No significant difference between exposure to 400 rad and 500 rad was seen.

2. In the nuclei of the epithelium and the young lens fibers, aggregations of the nucleoli were seen beginning 48 hours after irradiation. Tortuous, tapelike aggregation of the nucleolus was seen in one young lens fiber of the equatorial cortex four days after irradiation.

3. In the ciliary body, there were no changes seen which could be differentiated from an artifact. This simultaneous comparison of early radiation damage induced in the lens epithelium and the ciliary body during the latent period of radiation cataract suggests that the primary site of radiation injury is the lens.

4. Congestion of the conjunctiva and iris, and inflammation of the uvea were practically nonexistent in the fast neutron group, whereas these symptoms of injury were more severe in a group exposed to X rays.

5. The changes in the lens epithelium after fast neutron irradiation were much more marked than after x-irradiation when studied by means of the electron microscope.

Species variation of the lens epithelium to ionizing radiation. P. J. Leinfelder, M.D., and John Dickerson, M.D., Department of Ophthalmology, State University of Iowa, Iowa City.

Previous experiments by Dr. Leinfelder have shown that ground squirrels do not develop cataracts after large doses of X rays. Doses used were up to 2,000 r whole body and after one year there is no evidence of cataract on ophthalmoscopic examination. This led to our present study.

Unanesthetized ground squirrels were placed in a holder with their body strapped down and their neck firmly collared. They were covered with a lead casette so that only their eyes showed. They were given 5,000 r of 250 kv—30 ma, X rays with 0.25 mm. Cu and 1.0 mm. Al filtration. These animals were not hibernating. The eyes were examined prior to exposure and periodically after exposure. About 20 percent of the eyes were lost from radiation keratitis. The animals were sacrificed at three days, seven days, 14 days, one month, two months, three months, four months, and six months. There are three animals to be killed at nine months, one year and 18 months. After death the eyes were placed immediately in Carnoy's fixative for one to two hours and then the lens extracted. A whole mount was made of the lens epithelium and capsule and an occasional lens was sectioned.

After three days no mitoses were seen. After seven days there were some cells with pyknotic nuclei and lighter colored cytoplasm and were obviously dying. After 14 days there were many more pyknotic cells which were all located in the equatorial area. After one month we saw the first definite changes of radiation with the formation of multinucleated cells at the equator and more pyknotic cells. The cells did not show the characteristic nuclear extrusions or micronuclei seen in the mouse and rabbit. There were no mitotic figures seen.

At three months there were less pyknotic cells but now the epithelium had lost its regular appearance where these dead cells had dropped out and others had begun to fill in the void. At four months we began to see multinucleated cells in the central epithelium occasionally and many of these abnormal cells at the equatorial area. The

epithelium was difficult to remove from the cortex because it had become more firmly attached at the equator.

At six months we had the same picture, only more accentuated. For the first time there were mitotic figures and all of them appeared to have abnormal chromosomal patterns. It was at this time that we saw with the ophthalmoscope a minimal posterior polar punctate opacity which we considered due to irradiation.

Cross sections of the lens up to two months were normal. We have no cross section for three and four months. The sections of the six month eye show abnormal nuclei at the equator and some early abnormal lens fibers. These abnormal fibers are located only in the outer most layers and they are not the swollen fibers seen in other animals. The changes are minimal.

Five thousand r should be classified as a massive insult to the lens and we expected to have much more marked effects than have appeared. In mice and rabbits these doses produce early changes with micronuclei and abnormal mitoses throughout the entire epithelium and leading to a complete opacity within six months. There can be no doubt that these eyes have been affected but they have not shown the marked change one should expect.

A method of photographing fluorescence in circulating blood of the human eye. Harold R. Novotny, B.S., and David L. Alvis, M.D., Departments of Medicine and Ophthalmology, Indiana University School of Medicine, Indianapolis. Supported (in part) by contract AF41 (657)-225 monitored by the School of Aviation Medicine, Brooks Air Force Base, Texas, and (in part) by grants from the Life Insurance Medical Research Fund and the Knights Templar Eye Foundation, and (in part) by Public Health Service grant 2B5034.

The physiopathology of the retinal blood supply could be better understood if we knew more about the blood-flow rates in these vessels. Unfortunately, such data are incomplete, and a better method of studying these vessels is needed. Chao and Flocks have contributed a method of determining retinal circulation time by the vascular injection of trypan blue and fluorescein in cats.

As an approach to the problem, and the purpose of this paper, we wish to report a method of observing a substance circulating in the blood of the human retina after intravenous injection.

Essentially, the method was based upon the selective filtration of fluorescein luminescence and the photography of its emission from the retinal vessels during various phases of arteriolar and venous flow.

Photographs were made with the Zeiss fundus camera, using Ansco Super Hypan film and Kodak Wratten filters number 47, and number 58 with a 3.0 mm. layer of 0.25 M $CuSO_4 \cdot 5H_2O$.

Striking light intensity changes were found in the retinal vessels as the fluorescein passed through. Arteriolar and venous filling phases were evident in serial photographs. In both of these filling phases, definition was good enough to see streaming of the fluorescein along the walls of larger vessels. That is, columns of blood entering larger veins from the smaller tributaries apparently maintained their integrity, unmixed with the blood of that vessel.

A comparable streaming effect was seen in arteriolar fillings. A current of dye limited to one side of a large arteriole was directed into smaller branches.

Arteriolovenous shunts seemed evident in some areas.

Phasic filling of arterioles was suggested in serial photographs. Also, the persistent background mottling which developed, presumably represented the comparatively sluggish choroidal circulation.

These studies are being continued in order to overcome certain technical limitations and to apply them to the vascular changes in pathologic entities, such as diabetic and hypertensive retinopathy, occlusive vascular disease, and degenerative states.

The subretinal fluid: I. Analysis by paper electrophoresis. Robert C. Watzke, M.D., and Ann Steele, Department of Ophthalmology and Medical Research Center, University Hospitals, Iowa City, Iowa.

This is a preliminary report on the electrophoretic analysis of subretinal fluid obtained during scleral buckling operations for idiopathic retinal detachments.

Analysis of the protein components of subretinal fluid by electrophoresis has been the subject of several studies during the past decade. Such studies have demonstrated the presence of a relatively large protein fraction whose mobility corresponded to albumin and a relatively smaller component in the globulin range. The globulin component could be fractionated into various peaks depending on the method used. Finally, one investigator has demonstrated the occasional presence of an "X fraction" whose mobility placed it in the prealbumin range.

The subretinal fluid in the present studies was obtained from patients with idiopathic retinal detachments during the course of a scleral buckling procedure. During this operation, a choroidal knuckle under the detached retina was exposed and penetrated under ophthalmoscopic control. The subretinal fluid was collected in a lacrimal cannula and syringe and was kept free of all observable blood. Specimens were deep frozen until analyzed.

In order to avoid contamination of the subretinal fluid sample with blood, a benzidine test was set up and calibrated so that all specimens were discarded which showed a concentration of blood in excess of one part of hemoglobin per 20,000

parts of diluent. Serum protein in this dilution was not recordable in the electrophoretic apparatus used. Because the subretinal fluid sample was small, each specimen was analyzed for protein content by a Micro-Kjeldahl method. Protein was found to vary from 0.64 mg. per cc. to 2.77 mg. cc.

Paper electrophoresis was done with a Beckman-Spinco Model R, Series C cell using Schleicher and Schuell 2043-A paper strips. The usual Beckman-Spinco method of fixing and staining the protein components on the strips was followed. Strips were analyzed in a Beckman-Spinco Analytrol. This procedure has been previously used for serum and cerebrospinal fluid analysis and has been found to give reproducible results.

The electrophoretic analysis of subretinal fluid demonstrated the presence of a protein complex whose mobility placed it in the prealbumin range. This confirms the previous report of such a component by Hinz in 1956. While this worker found such a fraction to be present in some of his specimens, we found it to be present in all.

A large peak corresponding to serum albumin was found together with a smaller proportion of globulin whose components included peaks corresponding to beta and gamma globulin.

The presence of an "X fraction" or prealbumin component has previously been noted in normal cerebrospinal fluid and in bovine vitreous. Elucidation of this component and its relation to normal and abnormal human vitreous is in progress.

Flicker-fusion and luminosity functions in dichromasy. Gordon G. Heath, Ph.D., Indiana University, Bloomington.

Luminosity curves of protanopes, deuteranopes, and normal observers were determined by the critical frequency method at several photopic levels. In addition, F-log I_λ curves were determined at 14 wavelengths for intensities covering most of the functional range of the eye.

Data for the three groups of observers were compared specificially to determine whether deuteranopia, like protanopia, must be considered to be the result of absence of one of the important brightness-producing receptor-types present in normal color vision, an interpretation suggested by several recent studies of foveal threshold sensitivities and one which, because of the yellow and blue hues perceived by deuteranopes, would necessitate rejection of the three-component theory of color vision.

The scotopic sections of the F-log I_λ curves were found to be similar in slope and maximum height for the three groups of observers, but different in extent. Protanopes showed longer scotopic sections at long wavelengths than did normal or deuteranopic subjects.

For all observers, the scotopic-photopic transition was characterized at short wavelengths by a prominent dip in the F-log I_λ curve, indicating a decrease in subjective brightness accompanying an increase in stimulus intensity. It was concluded that this "mesopic dip" was a result of mutual inhibition of rod and cone activities in the intensity range where neither was favored over the other.

The photopic sections of all F-log I_λ curves for a given observer could be superimposed, indicating that curve slope was invariant with wavelength, but it was found that this treatment concealed marked slope changes occurring in the long wavelength curves of normal observers at moderate to high photopic levels, the level depending on wavelength. The bend was accompanied by a subjective report of a change in hue of the test light from red toward yellow. No such "yellow bend" was found with protanopes, and could not be established with certainty for deuteranopes.

The "yellow bend" marked the onset of a progressive reduction in the relative luminosities of long wavelength lights for normal observers, causing normal relative luminosity curves at high brightness levels to resemble those of protanopes. This was interpreted as an adaptational suppression or exhaustion of normal redness receptors due to intense long wavelength stimulation. This explanation is in accord with the finding that prolonged observation of a high-intensity red light by normal subjects caused its perceived hue to change to yellow and then to a vivid green. No evidence of similar adaptation effects involving other receptors was found.

Direct comparison of luminosity curves showed no loss of luminosity at photopic levels for deuteranopes, relative to normals, anywhere in the spectrum. Instead, a gain in luminosity was found throughout the region from about 520 mμ to the long wavelength end of the spectrum, the same region in which protanopes demonstrated considerably subnormal luminosities. These findings controvert the hypothesis of a loss basis for deuteranopia, but support the hypothesis for protanopia.

Size effects in simultaneous color contrasts. Ingoborg Schmidt, M.D., and Phillip E. Grush, Indiana University, Bloomington.

When observing two neutral gray circles, one subtending two degrees, the other 20 minutes of arc, on a green-yellow background by simultaneous contrast the larger circle appears purplish, the smaller brownish. On a yellow-red surround the larger appears bluish, the smaller greenish blue-green.

An attempt was made to determine this difference quantitatively for seven colored papers distributed about evenly around the white point C in the chromaticity diagram and serving as background for a larger neutral gray circle of two degrees and for a smaller neutral gray circle of 20 minutes visual angle. The value of the colored papers and the neutral grays was the same, namely 6/ in Munsell notations. The papers were of the highest chroma available at that value, namely /10 in the long wavelengths range and /8 in the

short wavelengths range. The observation time was 10 seconds. Two subjects determined in Munsell notations the contrast colors on the large and small neutral grays. The trichromatic coordinates of the matching Munsell samples were established from tables and the points entered into the chromaticity diagram. The findings of the two subjects showed fairly good agreement. The results obtained monocularly and binocularly did not differ significantly. The contrast to green-yellow shifted from purple on large to a redder or browner hue on small; that to blue-green from red-purple to more red or more yellow. The contrast to red-purple showed a shift from yellowish-green to more bluish-green, that to yellow-red from blue to greenish-blue-green. The contrasts to blue and yellow showed insignificant shifts or none at all. Thus, in general, purplish contrast colors changed to reddish, brownish, or yellowish. Yellowish-green and bluish changed to blue-green. Purplish-blue and yellow contrast colors did not show much change. The largest visual angle at which the contrast hue typical of the smaller gray circles became noticeable equaled about 1.5 degrees.

The color changes were very similar to those found on actual color stimuli of small subtense, a phenomenon known as tritanomaly of the fovea. It is very likely that the latter would also affect the perception of contrast colors. However, from a compilation of data by Farnsworth, it follows that under the luminance conditions of our experiments a tritanomaly would occur for color fields of maximally five minutes of arc. However, this limit has not been established yet for colors of such low chroma as were the contrast colors observed.

Another explanation may be the colored fringes produced by the irradiation from the contrast inducing color into the contrasting area. These fringes are due mainly to the chromatic and spheric aberrations of our crystalline lens. One could observe them more clearly on the large gray circles. They were of a width of about 1.0 mm., which from a distance of 40 cm. corresponded to about 10 minutes of arc. Thus these fringes would just cover the 20 minutes of arc of the small gray circles. One could imagine the contrast color as the result of observing the colored fringe through a filter equal in color to the induced contrast, for example, on a yellow-red background the fringe would appear yellow, the induced contrast a bluish blue-green. The result on small was a greenish blue-green. These colored fringes were abolished to some extent by observing through a pinhole of 1.0 or 2.0 mm. diameter, thus forcing the light rays to enter through the center of the lens.

It is possible that the small involuntary eye movements played a role in producing the differences in contrasts, since their effect would be more noticeable on the small than the large gray areas. Due to these movements the retinal area stimulated by the gray circle would be alternately stimulated also by the colored surround. This may have caused an intensifying of the contrast color by an after-image. However the difference in contrast color of the large and the small areas was present already at an exposure of 1/100 seconds, at which time the retina is practically immobile. One must conclude then that this difference was not caused by the small movements of the eye; it was not an after-image effect. Its presence at shorter exposures speaks in favor of the colored fringe theory since chromatic and spheric aberration are a constant physical property of the lens. But these observations do not rule out the trit-anomaly of the fovea as a possibility for an explanation.

The described effects have some importance in cases where small colored details are of interest, for instance microscopy or astronomy; for example, in observing the planet Mars. The findings may be helpful also to explain some controversial data about the colors of simultaneous contrasts in literature.

Spectral hue loci of normal and anomalous trichromates. Melvin L. Rubin, M.D., Department of Ophthalmology, State University of Iowa, Iowa City.

The main body of this work was established to examine Wall's hypothesis that anomalous trichromats may have any particular hue displaced to an abnormal wavelength as compared to a color normal. Minor objectives were to check Forbes' suggestion that there are two color-normal groups as regards to the qualitative sensation of spectral blue and spectral violet and, third, to examine Talbot's hypothesis that there were two groups of color-normals in respect to where they found pure green.

The subjects—278 normals, 12 protanomals, and 32 deuteranomals—were examined and required to locate as to wavelength the spectral hues yellow, orange, green, cyan and blue. The instrument used was a fixed arm monochromator with a constant deviation prism and afforded a central visual field of six degrees which could be half filled with essentially monochromatic light. The subject bracketed a subjectively unique color in a constant-brightness spectrum at two luminance levels, 10 mL and 1.0 mL. There was no significant difference in the data of the two luminance levels.

The standard deviations of the single hue setting for an individual observer were remarkably small. The mean wavelengths at which the three classes of subjects located the five hues and the standard deviations of these means was given. Forbes' idea that two color-normal populations exist as regards to the distinctivity between violet and blue was not substantiated. Deuteranomals, however, can not distinguish spectral violet from spectral blue.

Talbot's idea that there is a bimodal distribution among color normals for pure green is shown

to be true, with the specific loci at 525 mμ as he guessed, and the other at 514 mμ, which he guessed at 500 mμ.

The average deuteranomal finds pure yellow and mid-orange at somewhat longer wavelengths than does the average normal, and this can explain why the deuteranomal sets the anomaloscope the particular way he does. The average protanomal finds his pure colors at wavelengths shorter than the average normal. However, his displacements per se do not obviously account for his anomaloscopic performance.

Fluorescein-tagged antibody as an aid in laboratory diagnosis of herpes simplex eye infections. Robert R. Sexton, M.D., Department of Ophthalmology, University of Iowa, Iowa City.

The possible use of a fluorescein-tagged antibody technique as a rapid diagnostic aid in herpes simplex infection of the cornea was studied by the indirect method (Coons). Globulin was tagged with fluorescein by conjugation with isothiocyanate.

Rabbits were inoculated with herpes simplex virus. Both corneas were abraided and virus inoculated only in the right eye. After the first sign of keratitis smears were made of corneal scrapings from both the right (infected) and left (control) eyes.

The smears were reacted with antiherpes guinea pig serum, washed, and treated with antiguinea pig rabbit globulin which had been conjugated with fluorescein isothiocyanate. Both known positive and known negative slides were also treated with the fluorescein-tagged preparation without prior reaction with the antiherpes serum. This provided additional controls.

In the herpes simplex infected corneas small bright fluorescent areas were seen with regularity in the nucleus and cytoplasm of many epithelial cells. These were interpreted as being antigen-antibody complex.

The known positive and control slides all exhibited considerable nonspecific fluorescence. However, the controls did not show the areas of bright staining present in the known positives completely treated.

These preliminary studies indicate that this staining technique may be applicable in aiding with the definitive laboratory diagnosis of herpes simplex infections of the cornea. Reports can be available within two or three hours from the time the scraping is obtained.

The relationship of intestinal protozoa to uveitis. I. Menachof, M.D., C. Birch, M.D., B. Anast, M.D., and W. F. Hughes, Jr., M.D., Chicago.

The ophthalmologists' interest in the relationship between intestinal parasitic infection and inflammation of the inner eye was revived by the microscopic findings of amoebae in enucleated eyes by Kruemmel (1951) and by the report of Braley, et al., concerning a characteristic fundus lesion associated with intestinal amoebiasis (1957).

This study was undertaken with the hope of making a further contribution to the question of ocular amoebiasis by (1) reviewing the cases of uveitis which had a fecal examination in the course of their etiologic survey; (2) the examination of a control group of patients selected at random from the clinics at the Research and Educational hospitals; and (3) by inoculation of protozoa into the eyes of rabbits.

A brief résumé of the ocular findings in the cases reported by Braley is given. Seven cases treated with amebacidal agents at the University of Illinois are briefly described and the clinical similarities and differences between Braley's cases are pointed out. Not all patients had cystic macular lesions and only those patients with extramacular involvement had visual improvement.

A series of 137 patients with uveitis was examined and 5.8 percent had E. histolytica in the stool. A control group of nonuveitis patients had an incidence of 3.7 percent Endamoeba histolytica in their stool. These figures would fall into the normal incidence in sample populations as reported by other investigators.

Seventy pigmented rabbits were inoculated with E. histolytica, giardia lamblia and Endamoeba coli, into the vitreous body, suprachoroidal space, gastrointestinal tract and into the liver. Results were negative, as no lesions were produced when the protozoal organisms were free of bacterial contaminants.

The opinion of the authors is that no correlation exists at present in patients with uveitis and intestinal protozoa. However, in view of the response of a few patients in their series and those of Braley treatment may be indicated for these parasites.

The role of increased responsibility in the precipitation of endogenous uveitis in adults. Evelyn Dunbar, M.A., and T. F. Schlaegel, Jr., M.D., Indiana University School of Medicine, Indianapolis.

Since it had been noted that the onset of uveitis was often precipitated by or prolonged by "increased responsibilities," we attempted by case study and analysis to determine whether such "increased responsibility" is more common before the precipitation of uveitis than it is before the onset of other ocular and nonocular conditions.

As a part of their routine work-up both private and clinic patients were interviewed by the medical case worker; the interview was structured to cover the areas of responsibility and to explore feelings surrounding these. Responsibility was defined in a broad sense to encompass other pressure such as interpersonal problems and unemployment and all stresses were considered for the 12 months before the onset of the uveitis. Only the most recent attack was studied.

The same structured interview was conducted

with the control group including 21 nonocular male ulcer patients at Veterans Hospital; 22 eye problems often confused with uveitis; and 20 nonpatients who were spouses or other relatives of uveitis patients not included in the study. These three control groups were combined after a chi-square analysis showed there were no differences in the areas being studied.

The areas of responsibility studied were (1) increased hours of employment; (2) objective increase of responsibility in employment; (3) subjective increase of pressure in employment; (4) dissatisfaction with job and/or considering another job; (5) engaged or married; (6) pregnancy or birth of child; (7) financial worries; (8) interpersonal family problems; (9) illness or death in family; (10) school stress; (11) physical or financial support of others outside of immediate family; (12) negotiation for or purchase of home. We found it difficult to attach a quantitative value to the various stresses so each was given equal value.

Participants of the uveitis and control groups compared closely in age, sex, education, employment, sibling rank, number of children and marital status. The majority of participants were or had been married; there were slightly more men than women. Most of the participants were in the 20-50 year age group. There was a significantly larger number of uveitis patients than control patients younger than 45 years as compared to older than 45 years. There was a trend for uveitis patients to have had more education than the controls.

There was a significantly larger number of control participants who denied stress, indicating that control participants either have fewer stresses or deny stresses more readily than uveitis patients who had, or claimed to have, a significantly greater number of stresses than the control participants. Comparing uveitis and control groups stress by stress there were no instances in which the differences as calculated by the chi-square technique reached the five-percent level of confidence. The five-percent level was approached, however, in regard to the "engaged or married" category.

The fact that when the stresses were considered singly there were no differences, but when the total number of stresses were compared there was a significant difference would tend to indicate that the important consideration in differentiating the two groups was the accumulation of stresses and not their type. However, our impression in dealing with uveitis patients was that certain stresses such as engagement or marriage may be more important than other types.

The Minnesota Multiphasic Personality Inventory in adults with uveitis. Eugene E. Levitt, Ph.D., and T. F. Schlaegel, M.D., Departments of Psychiatry and Ophthalmology, Indiana University Medical School, Indianapolis.

This paper describes a continuation of an investigation of the possible relationship between psychopathology and uveitis. The original study of 48 cases (Schlaegel and Levitt, Am. J. Ophth., 48:312-316, 1959) found a significant relationship between uveitis and psychopathology as measured by the Minnesota Multiphasic Personality Inventory, a well-standardized verbal scale. Forty-four percent of the subjects had pathologically elevated scales, where 20 percent is the chance expectancy. No relationship was found with sex, or with severity, site, or type of inflammation.

A second sample of 40 cases was then studied. This group (Sample B) yielded entirely negative results, though it was simply a continuation of the original sample (Sample A), and did not differ from it descriptively. Only 20 percent of this group showed pathologic scales. A difference which could possibly have accounted for the discrepancy in results was the administration procedure.

The data of Sample A had been collected by a social worker, while those of Sample B were collected by a receptionist. Unwillingness of the subjects to reveal psychopathology to a nonprofessional could have caused the negative results of Study B.

To test this, a third sample (Sample C) of 23 cases was tested. The MMPI was administered by the receptionist, but the subject then sealed the test protocol in an envelope stamped, "Confidential data, etc."

In this group, 35 percent of the cases showed pathologically elevated scales. This percentage, though closer to that of Sample A than to Sample B, does not differ significantly from the chance expectation. However, a control group of 32 patient spouses and other eye cases was collected along the way. Samples A and C had significantly higher incidence of psychopathology than did the control group, while Sample B did not.

On this basis, we assume that the test administration procedures biased Sample B and that its results are invalid. Pooling Samples A and C yields an incidence of psychopathologic scales of nearly 41 percent against the chance expectancy of 20 percent. The difference is highly significant. This incidence is also significantly greater than that for the control group.

In Sample C, a significantly greater number of cases with psychopathology had granulomatous infections with a posterior, or both anterior and posterior, site. There was no relationship with severity; the biserial correlation is 0.12. However, when we pool Samples A and C, the relationships with site and type of infection become nonsignificant. The correlation with severity ($r_{bis} = 0.18$ pooled or 0.17 averaged) is also nonsignificant. No relationship with sex appears in either sample. This continuation of our data collection reinforces the hypothesis that uveitis and psychopathology are related. The nature of the relationship—its causal factors— remains unknown.

The value of the Middlebrook-Dubos hemagglutination test for tuberculosis when run on aqueous samples of eyes with granulomatous iridocyclitis. T. F. Schlaegel, Jr., M.D., J. L. Arbogast,

M.D., and L. A. Estela, A.B. (with the technical assistance of K. Kimura, M.D., E. Dritsas, M.T. and D. Godwin, A.B.), Indiana University School of Medicine, Indianapolis.

Since the potential practical value of the Middlebrook-Dubos test on aqueous humor lies in its possible ability to differentiate tuberculous from nontuberculous iridocyclitis, these two types of uveitis were produced in the same rabbits previously given systemic tuberculosis by injection into the groin. After four weeks the anterior chambers were injected either with tubercule bacilli or with horse serum. Horse serum was used as a control agent to produce a nonspecific granulomatous iridocyclitis.

The Middlebrook-Dubos test was run on the blood serum at weekly intervals for the four weeks before and the four weeks after the injection into the eyes. Primary aqueous was collected before the intraocular injections and weekly thereafter for four weeks. If the aqueous titers for tuberculosis are simply a result of transudate from the blood, the aqueous humor titers should correlate only with the severity of the iridocyclitis which has been produced.

At one week after the intraocular injections there was no correlation of the aqueous titers with either the severity of the iridocyclitis or with the agent injected. After this first week, however, the high aqueous titers were definitely correlated with the injection of tubercle bacilli into the eye and not with the severity. A titer of ⅛ or above diagnosed the presence of tuberculous iridocyclitis in this experimental group of rabbits without resulting in any false positives. On the other hand false negatives were found in that many of the eyes receiving tubercle bacilli had titers below ⅛.

There were 34 patients who had both their aqueous and serum tested by the Middlebrook-Dubos technique. There were positive serum titers for tuberculosis in 77 percent of our cases diagnosed as tuberculosis and in 78 percent of those considered not tuberculous. A study of the aqueous titers, however, revealed that 75 percent of those considered tuberculous had positive titers as compared to 15 percent of those considered not tuberculous. Among granulomatous patients, 72 percent had positive serum titers as compared to 68 percent of the nongranulomatous cases. The aqueous titers, however, revealed twice the percentage in the granulomatous as in the nongranulomatous group; 28 percent as compared to 14 percent. The serum titers were positive in 62 percent of our patients with a positive isoniazid response as compared to 69 percent of those with a negative response. The aqueous humor, however, was positive in 80 percent of those having a positive isoniazid response as compared to 19 percent of those having a negative test.

Thus the aqueous test appears to be of value in helping differentiate between those cases which are tuberculous and those which are not tuberculous, whereas the serum Middlebrook-Dubos test is without any value in this regard.

Ophthalmic Miniature

Salt retention

Dear, do not weep—
Since recent years
It is more wise to keep
A watch on tears:

Some seek to analyse
With callow art
An easy pathway from your eyes
Into your heart

While others feel
That tears are nothing fine
And have no power to heal
More strong than lysozyme.

Besides, you should not grieve
But keep your sorrows pent—
There's not a man can quite forgive
Embarrassment.

From *The Lancet*,
April 23, 1960, p. 921.

AMERICAN JOURNAL OF OPHTHALMOLOGY

Published Monthly by the Ophthalmic Publishing Company

Address original papers, other scientific communications including correspondence, also books for review to *Dr. Derrick Vail, 700 North Michigan Avenue, Chicago 11, Illinois;* Society Proceedings to *Mrs. Katherine F. Chalkley, Lake Geneva, Wisconsin.* Manuscripts should be *original copies,* typed in *double space,* with wide margins.

Exchange copies of the medical journals should be sent to *Dr. F. Herbert Haessler, 561 North 15th Street, Milwaukee 3, Wisconsin.*

Subscriptions, application for single copies, notices of changes of address, and communications with reference to advertising should be addressed to the *Manager of Subscriptions and Advertising, 664 North Michigan Avenue, Chicago 11, Illinois.* Copy of advertisements must be sent to the manager by the 10th of the month preceding its appearance.

Change of address notice should be received not later than the 10th of the month prior to the issue for which the change is to go into effect. Both old and new addresses should be given.

Author's proofs should be corrected and returned within forty-eight hours to the *Manuscript Editor, Mrs. Katherine F. Chalkley, Lake Geneva, Wisconsin.* Fifty reprints of each article will be supplied to the author without charge. Additional reprints may be obtained from the printer, the George Banta Company, Inc., Curtis Reed Plaza, Menasha, Wisconsin, if ordered at the time proofs are returned. But reprints to contain colored plates must be ordered when the article is accepted.

1960 AMERICAN OPHTHALMOLOGICAL SOCIETY

The 96th annual meeting of the American Ophthalmological Society took place in the Broadmoor Hotel, Colorado Springs, Colorado, from May 16 to 18, 1960. One hundred and seven members and 57 guests attended. The setting and arrangements were beautiful, adequate and comfortable but the weather was a little unkind and subdued to some extent the usual outdoor activities.

Algernon B. Reese, M.D., of New York, presided with wit, grace and charm. His firm and impartial fairness in keeping the essayists and the discussors strictly to the established time limits earned the respect and gratitude of all those present.

The scientific program seemed to be unusually good this year. It consisted of 19

papers, each most skillfully presented and illustrated. It is a pleasure to see the precision and care that was exhibited by the speakers in presenting their contributions. Even the discussors fell into line as if rehearsed ahead of time.

Albert E. Sloane, M.D., of Boston led off with a discussion of "school vision." A pioneer in the visual screening of school children and mainly responsible for the development of the Massachusetts Vision Test for this purpose 25 years ago, he reviewed the subject and described and evaluated new instruments and practices introduced in this country most recently. He pointed out that the health authorities in many of our States are confused and uncertain what to do in this field. His paper sets up "working plans for eye testing programs" and discusses methods of keeping them up to date. A lively discussion ensued and, as a result of Dr. Sloane's recommendations, moves to form a joint national committee with members of other ophthalmic societies were made. Its purpose would be to standardize and guide nationwide studies in this field. This is a wise and constructive move.

T. E. Sanders, M.D., of Saint Louis, exhibited the subject of "Intraocular nevoxantho-endothelioma (juvenile xanthogranuloma)." This rare disease is characterized by lipoid nodules in the iris, most always of infants, associated with typical skin lesions. The author reported on a careful clinical and histopathologic study of three personal cases and 17 other authenticated cases of other ophthalmologists and from the Armed Forces Institute of Pathology. Unless treated, the affected eyes become lost due to hemorrhages and glaucoma. Treatment with X rays, given in doses of 100 r every two weeks to a total of 400 r, seems to offer hope.

Arthur Gerard DeVoe, M.D., of New York, gave a play-by-play description of the constant treatment by steroids of a patient with sympathetic ophthalmia for over six years. The patient was 12 years of age when his right eye was injured with a BB shot. Later a linear extraction of a traumatic cataract was performed which led to the onset of sympathetic ophthalmia. Repeated courses of general and local steroid (all available forms) therapy was continued for more than six years and in spite of the development of Cushing's syndrome and decalcification of vertebral bodies, which gave considerable concern. These serious complications were skillfully handled and, as of now, the patient has maintained normal vision, in spite of an occasional and usually mild flare-up.

Banks Anderson, M.D., and his son, Banks Anderson, Jr., M.D., of Durham, North Carolina, described the "reaction of ocular tissues perfused with nitrogen mustard or similar alkylating agents incidental to the treatment of inoperable malignancies in adjacent structures." This was a fascinating discussion of what happens to the ocular tissues when perfusion of inoperable cancers with mustard compounds in amounts two to three times the minimal lethal dose is used. This is only possible to do when the involved area is isolated and has its own blood supply. The experience in a small number of cases (15) seems to show that the eye has a lower tolerance to the drugs than was anticipated. Post-mortem eyes showed that the choroidal vessels were involved more than the retinal vessels. The authors concluded that the relative importance of preservation of vision may be a limiting factor in this form of treatment.

Brendan D. Leahey, M.D., of Boston, gave us the "Criteria for early surgical correction of esotropia in infants and young children." By young children he meant even infants of 10 months. He advocated immediate surgery in suitable cases, based on the fusion potential estimated as the ratio of the duration of the squint to the age of the child. This was a thought-provoking article, fully supported by Phillip Knapp, M.D., of New York, the chief discussor. Approval of the premise was reserved by the members of the audience, for the most part.

John M. McLean, M.D., and (by invitation) one of his residents, Miles A. Galin, M.D., presented "Studies in osmotic pressure relationships." The paper was most admirably given by Dr. Galin who described osmotic studies on the blood of glaucoma patients and volunteers and experimental studies in dogs. This fundamental paper was superbly discussed by Francis H. Adler, M.D., of Philadelphia.

Guillermo Pico, M.D., of San Juan, Puerto Rico, described in detail a case of "chronic pseudotumoral edema of bulbar conjunctiva of myxedematous amyloid degeneration." This was an interesting and potentially important paper, of a hitherto unrecognized association of diseases, particularly as concerns the eye.

Frederick C. Blodi, M.D., and (by invitation) R. D. Whinery, M.D., and C. A. Hendricks, M.D., of Iowa City, Iowa, presented "Lipid proteinosis (Urbach-Wiethe) involving the lids." This is a rare hereditary disease, well recognized by dermatologists and laryngologists. No case has up to now been reported in the ophthalmic literature, which is surprising for the authors found that more than 75 percent of the reported cases have characteristic and pathognomonic involvement of the lids. This consists of rows of yellow-white papules which appear along the lid margins and increase in size or coalesce to form large tumors, so that finally the entire lid margins are involved. The authors presented a typical case that was extensively studied. The lid lesions revealed a deposition of a sort of "ground substance" that could be stained with Fat Oil and was PAS positive.

One of the most outstanding papers of the meeting was given by Michael J. Hogan, M.D., and (by invitation) Chieko Yoneda, M.D., Ann Lewis, B.A., and Phyllis Zweigert, of San Francisco,who spoke on the life, habits and composition of the sporozoa Toxoplasma. Their beautiful slides gave us an unforgettable experience. Their studies have markedly advanced our knowledge of the morphology and biology of the parasite.

The next two papers revived an age-old controversy on the surgery of congenital cataracts and, when it was all over, we are about where we were before. Ira S. Jones, M.D., of New York, defended the needling operation and Frederick C. Cordes, M.D., of San Francisco, the linear extraction. A lively discussion occurred and very likely there were few converts made to either side.

Robert N. Shaffer, M.D., of San Francisco, presented us with a "new classification of the glaucomas." It was a carefully considered and all-embracing classification that may be most useful, particularly when correlated with medical and surgical treatment.

H. Rommell Hildreth, M.D., of Saint Louis, spoke on "Digital ocular compression preceding cataract surgery." He presented evidence to show that the hypotony that is produced is probably due to a relative reduction in vitreous volume, although temporary stretching of the sclera or emptying of the choroidal bed may be factors, too.

Arthur J. Bedell, M.D., of Albany, New York, gave us one of his usual illuminating Kodachrome talks on an unusual case of progressive bilateral choroiditis observed and recorded over a period of 18 years.

Phillips Thygeson, M.D., M. J. Hogan, M.D., and (by invitation) S. J. Kimura, M.D., San Francisco, in their paper on "Unfavorable effect of topical steroid therapy of herpetic keratitis," presented indisputable evidence of the devastating effect of the use of this drug in this condition. They said: "In this disease the dangers inherent in the use of steroid therapy far outweigh any anti-inflammatory benefits that may be obtained." George N. Wise, M.D., of New York, gave an informative and well-illustrated paper on "Uveitis with secondary arteriosclerosis." Leonard Christensen, M.D., of Portland, Oregon, discussed most comprehensively "Postoperative epithelization of the anterior chamber," and showed excellent photomicrographs in illustration.

Hermann M. Burian, M.D., and (by invi-

tation) Gunter K. von Noorden, M.D., and I. V. Ponseti, of Iowa City, Iowa, gave us a new idea in their paper on "Chamber angle anomalies in systemic connective tissue disorders." Gonioscopic studies of otherwise normal eyes reveal various abnormalities, such as strands of pectinate ligament fibers, iris processes, abnormal vessels and lumplike formations, as well as localized stromal defects in the extreme periphery of the iris. They advanced the premise, with considerable evidence, that these abnormalities are but a part of generalized systemic disorders (for example, Marfan's syndrome, idiopathic scoliosis, Perthe's disease, and so forth). If verified, this observation will assume considerable clinical significance.

The final paper of this stimulating program was by A. E. Maumenee, M.D., of Baltimore. He discussed the broad problem of "External filtering operations for glaucoma: The mechanisms of function and failure." There are three causes for failure of the operation he told us. These are internal blockage of the scleral opening, closure of the scleral wound, and failure of Tenon's capsule and conjunctiva to absorb aqueous. The first two involve the matter of surgical technique. Our attention should, therefore, be directed toward a study of Tenon's capsule in relation to the overlying conjunctiva. This he proceeded to do in excellent fashion.

The social activities, somewhat inhibited by the uncertain weather, were active and pleasurable. The president's reception to the new members was gracious and sparkling. Friends and colleagues of Arthur J. Bedell and Francis H. Adler joined forces in a delightful reception and cocktail party in their honor. The second afternoon was devoted to a sight-seeing trip to the lavishly beautiful United States Air Force Academy a few miles distant. Our host was Col. Richard S. Fixott (MC) U.S.A.F., in charge of ophthalmology at the Academy. It was a most impressive experience. The Tuesday evening picture show was delightful.

Maynard C. Wheeler, M.D., of New York, most able and efficient secretary of the society, retired from this office after 12 years of devoted service. As a token of the appreciation for this service, the council, through President Reese, presented him with a piece of silver.

The new officers elected are: President, Edwin Blake Dunphy, M.D., of Boston; vice president, Francis Heed Adler, M.D., of Philadelphia: secretary-treasurer, Joseph A. C. Wadsworth, M.D., of New York City; member of the council, Gordon M. Bruce, M.D., of New York City. The 1961 meeting of the society will be held in May at the Homestead, Hot Springs, Virginia. The first Frederick H. Verhoeff Lecture in Ophthalmology will be given at this meeting by Arthur J. Bedell, M.D., of Albany, New York.

The Lucian Howe Gold Medal was awarded to Derrick T. Vail, M.D., of Chicago (who was overwhelmed and speechless by this great honor) "in recognition of his distinguished service to ophthalmology."

Naturally, I think it was the best meeting that the society has ever held.

Derrick Vail.

OBITUARIES

HANS BARKAN
(1882-1960)

With the death of Hans Barkan on March 7, 1960, San Francisco lost one of its most distinguished and beloved ophthalmologists. Hans Barkan was born in San Francisco July 26, 1882, the oldest son of Adolph and Louise Desepte Barkan. He was a member of a family that has been associated with ophthalmology. His father, Adolph, a Hungarian immigrant, was a member of the original medical faculty at Stanford University Medical School. His brother, Otto, who died in April, 1958, was widely known for his work in glaucoma. A nephew, Thomas Barkan, has just entered the private practice of ophthalmology.

Hans Barkan was a graduate of Stanford University and received his M.D. degree from Harvard Medical School in 1910. Following this he went to Vienna where he studied a number of years under Ernst Fuchs and then returned to this country to teach pathology at Harvard.

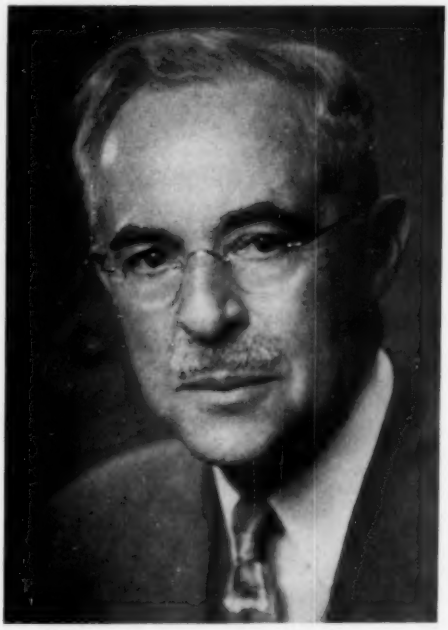
He returned to San Francisco as a practicing ophthalmologist in 1914 and continued to practice until his retirement in 1954. During the time that he was in active practice he wrote numerous articles on ophthalmologic subjects, in addition to being one of the editors of the *Archives of Ophthalmology*, and also for the *Excerpta Medica*. It was at this time that he served as Captain in the United States Army Medical Corps during World War I.

From 1925 to 1950, he was professor of ophthalmology and head of the Department of Ophthalmology at Stanford University Medical School. He was a great teacher who had the ability to keep his students spellbound during his lectures. It was with great affection that those who studied under him referred to him as "Doctor Hans." He enjoyed a large practice, was loved by his many patients and held in high esteem by his colleagues. As one of his former residents summed it up . . . "He was a great doctor, one who knew the depth and breadth of human nature, one who caused patients to say . . .'that man is a saint.'"

Dr. Barkan was also a music lover. An amateur violinist, he often played with friends from the San Francisco Symphony Orchestra. He was the author of a book *Brahms and Billroth: Letters from a Musical Friendship* and had served as a member of the San Francisco Symphony.

He was a member of numerous medical societies including the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology, the German Ophthalmological Society, and the Viennese Ophthalmological Society.

That he was interested in education is shown by the fact that he was a Trustee of Mills College, and of Thatcher School at Ojai.



HANS BARKAN, M.D.

Dr. Barkan is survived by his wife, the former Phoebe Bunker; two children, A. William Barkan and Mrs. Phoebe B. Gilpin; a brother Fritz Barkan, all of the San Francisco Bay area, and a sister Mrs. Eric Offerman of Zurich, Switzerland.

A man with many interests, capable in many fields, Hans Barkan enjoyed a full life.

Frederick C. Cordes.

HORACIO FERRER
(1876-1960)

The world mourns the passing, on March 6, 1960, of Dr. Haracio Ferrer, outstanding ophthalmic surgeon, soldier of Cuban independence, civic leader, and beloved, gentle pater familiae. Born in Union de Reyes in the province of Matanzas, Cuba, on March 4, 1876, his family traced its ancestry in Spain

to the 12th century, with physicians in its roster of notables since the 17th century. Both grandfathers were doctors. The death of his father, Dr. Benito Jose Ferrer y Toledo, when Horacio was five years of age, left his mother, the former Dolores Diaz Galvez, to care for his older brother, Virgilio, and himself.

His studies at Matanzas were interrupted by a period of military service in the Cuban war for independence. The youthful Horacio and his brother joined the forces of General Maximo Gomez in Camaguey in July, 1895. On August 13, 1895, Horacio Ferrer was seriously wounded in the face in the assault on the fort of Baga. Taken to the Bahamas and then to New York for reparative surgery, he recovered and returned to Cuba to take part in major engagements of the war. After the signing of the peace treaty at Washington on August 12, 1898, the brothers Ferrer returned to civil life.

After graduating in medicine from the University of Havana in 1901, Dr. Ferrer served as Military Public Health Officer, doing general surgery until 1910, when he devoted himself to ophthalmology.

Married to Tasita Paisan, he left five daughters, Olga, Bertha, Martha, Tasita, and Piedad. Dr. Olga Ferrer Sklar has followed in the footsteps of her famous father and has continued his ophthalmic practice.

Dr. Ferrer received many decorations and honors from a grateful government, as well as medals from the Cuban and Spanish Red Cross and the Republic of Mexico.

Before specializing in ophthalmology, he published valuable studies on the "ophthalmo-reaction of Calmette," on the diet of Cuban workers, and statistics of typhoid vaccinations in Cuba. He wrote biographical papers on Dr. Carlos Finley, Osvaldo Cruz and Enrique Lopez. His interest in the history of ophthalmology was life long. He possessed a collection of eyeglasses which had belonged to well-known Cuban men and women. In 1924, on the occasion of his admission to the Academy of Sciences of Havana, he gave a historical paper dealing with the contribution of Cuban ophthalmologists to the progress of ophthalmology. His book, *Con el Rifle al hombro* is an autobiographical record.

A busy clinician and ophthalmic surgeon, he also made many valuable contributions to the literature. His first paper in the field of ophthalmology dealt with the visual acuity of members of the regular army (1908). In 1912, Dr. Ferrer recorded the results of his ocular examination of 9,000 children. He reported, in 1932, the results in the first four cases of retinal detachment treated surgically in Cuba. In 1939, he presented a new instrument for cataract extraction by suction. His numerous writings included the subjects of optic atrophy after pituitary tumor, cataract, dacryocystitis, proliferating retinopathy, therapy of ocular tuberculosis, aniridia, glaucoma, and the use of sulfa drugs and penicillin in ophthalmology.

Dr. Ferrer was one of the founders of the Pan-American Association of Ophthalmology, and he attended its first meeting in Cleveland on October 11 and 12, 1940. He was a member of the Mexican and French Ophthalmological Societies.

The Instituto Horacio Ferrer of Havana, Cuba, was established in honor of the country's leading ophthalmologist. The first publication of this organization, printed early in 1960, contains many of the papers of Dr. Ferrer and much biographical material.

Through the late Dr. Charles H. May, I had the privilege and honor of meeting Dr. Ferrer and his family and of visiting his offices in Cuba. His unfailing enthusiasm for ophthalmology, his patience and courtesy with patients, friends and colleagues, his devotion to this family, and his life-long labors for democracy in his country, reveal the portrait of a great man.

Charles A. Perera.

CORRESPONDENCE

Ocular onchocerciasis

Editor,
American Journal of Ophthalmology:

May I correct a false and misleading statement by Dr. F. C. Rodger in The Journal (49:128 [Jan.] 1960.)

Rodger wrote "Ridley does not emphasize sheathing of the retinal vessels, an observation on which Sarkies, Toulant and Boithias, and Budden lay great stress. Most authors will agree this sign is nonspecific and of little value as an aid to diagnosis."

Ridley wrote (Ocular onchocerciasis, Brit. J. Ophth., Mono. Suppl. 10, 1945): "Perivascular sheathing chiefly around the veins was frequent."

The only reference to sheathing in my paper under reference (Natural history of onchocerciasis. Brit. J. Ophth., **41**:214, 1957) was: "The retinal blood vessels are often narrowed and may be sheathed for up to two disc diameters beyond the disc." This statement was similar to that of Ridley.

In Northern Nigeria I have found that amongst persons with onchocercal choroidoretinal lesions, sheathing was present in 28 percent of 339 persons examined in the course of total populations surveys, and 35 percent of 283 hospital patients. The figures are similar to those of Rodger for he states (Brit. J. Ophth., **42**:26, 1958) that in his survey he found sheathing was present in 23 percent of 94 "posterior degenerative" lesions and that it was slightly more common in the "exudative type" of onchocercal choroidoretinal lesion.

Although physiologic sheathing does occur in normal African eyes, I would put the rate much lower than the 10 percent quoted by Rodger (Brit. J. Ophth., **42**:26, 1958). For example, I did not find a single instance in the fundi of 386 persons who made up the total population in two widely separated villages of North Nigeria where onchocerciasis was not endemic. The pathologic sheathing associated with onchocerciasis is usually more extensive than the physiologic and is associated with narrowing of the retinal vessels. I therefore believe that sheathing, when present, is a sign of some value.

However, there is no substance in Rodger's statement that I laid great stress on this sign or his implied suggestion that I considered it specific.

(Signed) F. H. Budden,
Government Ophthalmologist,
North Nigeria.

Occlusion of cilioretinal artery

Editor,
American Journal of Ophthalmology:

In the article of Dr. Wallace Friedman on "Occlusion of the cilioretinal artery" which was published on page 684 in the May, 1959, issue of The American Journal of Ophthalmology, the author stated that he was unable to find a previously reported case. I reported two typical cases in the *Revista de Medicina y Ciencias Afines* (Buenos Aires) pages 45 and 215, No. 1 and 2, 1945.

(Signed) Héctor M. Nano,
Buenos Aires, Argentina.

Color sense in pregnancy

Editor,
American Journal of Ophthalmology:

Dr. Schiff-Wertheimer, before her recent demise, corresponded with me in regard to a curious case. A woman artist, who had just sold one of her efforts, was asked by the client why the colors on the left side of the painting were especially vivid. She then realized that during her pregnancies she worked with artistically brighter colors than normally. In this case the particularly brilliant color was yellow. No perimetric studies of colors were made but Dr. Schiff-Wertheimer agreed with my suggestion that such studies in pregnancy would be very much worth while and might throw some further light on the functional changes in the pituitary gland

consequent to pregnancy. As I am personally unable to carry on this research, I ardently hope that some younger confrere may be inspired to do so.

(Signed) Theodor Fischer-Galati, M.D.
Andover, Massachusetts.

BOOK REVIEWS

WORTH AND CHAVASSE'S SQUINT. By T. Keith Lyle, C.B.E., M.A., M.D., etc., and G. J. O. Bridgeman, M.S., M.A., M.B., etc. London, Baillière, Tindall and Cox, 1959, ninth edition. 382 pages, 214 figures, index. Price: $10.00. (The Williams and Wilkins Company, Baltimore, Maryland, exclusive United States agents.)

Very few indeed are the ophthalmologists in the world who do not know of the first edition by Claud Worth that appeared in 1903 and the subsequent editions, especially the seventh written by Bernard Chavasse, who introduced many new concepts, most of them widely accepted by now. The eighth edition was edited and revised in 1950 by T. Keith Lyle, a world-wide authority on ocular motility even then.

In the present edition, Lyle and Bridgeman, who is surgeon and medical officer in charge of the Orthoptic Department, the Western Ophthalmic Hospital (St. Mary's) and ophthalmic surgeon, St. George's and the Victoria Hospital for Children, have indeed "produced a textbook which is lucid and practical and, as far as possible, fully up to date" (quoted from the preface of the ninth edition). The well-known book has been rewritten and rearranged, simplified and enlarged. The illustrations are apt and informative at a glance. The book is well printed on excellent paper.

In the last nine years since the eighth edition appeared, advances and many changes in our interpretation of ocular muscle imbalance have taken place. It would, of course, be ungracious here to point out the marked influence that the American "muscle men" have had on these changes. The authors do take note of some of them. The approach, however, is in the traditional British manner, but that is a very good thing indeed. While some of us, therefore, may not agree with some of the thoughts that are expressed here, many of these critics do not agree among themselves, either, for the subject is complex and wide open for further investigation.

If you master the information contained in this work you will be a very good "muscle man" yourself and your diagnostic and surgical results will be every bit as satisfactory as those of the other fellow.

For those who are already experts, this volume will supplement their knowledge and give them further food for reflection and perhaps change. It is recommended to all ophthalmologists.

Derrick Vail.

SQUINT AND ALLIED CONDITIONS. George P. Guibor, M.D., D.D.S. New York, Grune and Stratton, 1959. 341 pages, 103 illustrations, bibliography, index. Price: $11.50.

George P. Guibor, associate attending ophthalmologist, Children's Memorial Hospital, Chicago, Illinois, has had an enormous clinical experience of over 25 years in the study of more than 41,500 patients with squint. During this time, he has pondered and mulled over the many complex problems involved. His lectures and papers before our societies have always been popular and informative. His clear logic and lucid expression have converted many skeptics to his original views and made many others stop, look and listen. While there are some facets of his presentation where there is considerable disagreement, for example, his strong support for the nonsurgical treatment of squint, such is the strength and clinical support of his arguments that we must listen to him, if we are to improve our muscle work.

This is a well-written and seriously thought-out book, full of illustrative case reports that stir our interest. The author em-

phasizes again and again the importance of an accurate diagnosis based on most meticulous and detailed analysis of the problem. This in turn is based on an intimate knowledge of the anatomy and neurophysiology that are involved.

The chapters on the objective examination of patients with squint, the functional examination of the eyes, amblyopia, anomalous correspondence, the use of prisms, occlusion and fusion training are particularly good and command respect.

Derrick Vail.

HANDBOOK OF PHYSIOLOGY, SECTION I: NEUROPHYSIOLOGY, VOLUME II. Edited by John Field, H. W. Magoun and Victor E. Hall. Baltimore, Maryland, Waverly Press Inc., 1960. 660 pages. Price: $20.00.

This is the second volume of the *Handbook of Physiology* published by the American Physiological Society. It is also the second of three volumes which will be devoted entirely to *Neurophysiology*. The first volume, which was reviewed in THE JOURNAL in January, 1960, covered the major part of visual neurophysiology. The present book has two major sections: "Motor mechanisms" and "Central regulatory mechanisms." The former of these two sections contains this book's only chapter which is primarily concerned with the neurophysiology of the visual system. It is entitled: "Central control of eye movements" and is written by D. Whitteridge, Edinburgh University, Scotland. The chapter begins with an account of the anatomy and physiology of the extraocular muscle fibers, nerve fibers and nerve endings. There is a detailed presentation of the much discussed proprioception of the extraocular muscles in animal and man, a field where the author has personally made major investigative contributions. Also included in this chapter are discussions of: (1) reflex control of eye motions, (2) nystagmus, (3) the importance of the superior colliculi in animals and man and (4) eye movements and visual cortex. The author concludes with an interesting section about eye motions in man and their importance for visual performance.

That minor portion of this lengthy text specifically concerned with visual physiology provides a thorough and useful review of a subject important to ophthalmologists. A good bibliography is also provided.

Christina Enroth.

SOCIAL CASEWORK AND BLINDNESS. By S. Finestone, Ph.D., F. Lowry, I. Lukoff and M. Whiteman, M.D. New York, American Foundation for the Blind, 1960. 157 pages. Price: $2.75 (hard cover), $1.50 (soft cover).

The volume, which emanates from the Research Center, New York School of Social Work, Columbia University, in co-operation with the American Foundation for the Blind, should stimulate the community to a greater awareness of the blind person's needs and of the services required to meet them adequately. In the population of the United States, one in 500 is legally blind. Of this number 10 percent are under the age of 21 years, while 50 percent or more are over 65 years of age. This monograph will be useful to both trained and untrained workers in agencies of all types that deal with the blind. Its viewpoint should be helpful also for casework with persons having other handicaps. Because of space limitations, discussion is restricted to casework practice with adult blind clients. The guiding principle throughout is that all blind persons who can work should be given an opportunity to do so in accordance with their aptitudes and abilities, and should be provided with the necessary training.

James E. Lebensohn.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

1
ANATOMY, EMBRYOLOGY, AND COMPARATIVE OPHTHALMOLOGY

Jankovsky, Franz. **A new method for embedding eyes rapidly.** Arch. f. Ophth. **161**:399-404, 1959.

The author describes a method of embedding eyes in celloidin-paraffin for histologic preparation which can be accomplished in three weeks. The sections are as good as sections made with the usual method of embedding in celloidin which takes four to six months. (4 figures)

F. H. Haessler.

2
GENERAL PATHOLOGY, BACTERIOLOGY, IMMUNOLOGY

Adamantiadis, B. **A severe case of medication allergy involving the eye.** Arch. d'opht. **19**:858-860, Dec., 1959.

The author describes the case of a young girl who had a history of mild allergic conjunctivitis and developed a severe medication reaction after removal of a foreign body. Coincidentally with the anterior involvement, there developed a central relative scotoma due to edema of the macula, with a drop in vision to 0.1. Adamantiadis then discusses the subject of medication allergy from topical use of drugs, with particular reference to deep involvement. P. Thygeson.

Merté, Hanns-Jürgen. **Experimental study of several problems of corneal anaphylaxis.** Arch. f. Ophth. **161**:420-465, 1960.

The data gathered by the author in the course of his extensive experiments are perspicuously tabulated. It was found possible to call forth keratitis anaphylactica by intracorneal injection of denatured corneal protein. This was also true when the protein used had its origin in the animal's own cornea. Repeated intracorneal injections of killed lues spirochetes brought about an anaphylactic corneal reaction. The injection of spirochetic antibodies into the cornea of rabbits infected with lues did not give rise to any reactions in the cornea. Processes such as those which Elschnig and Igersheimer assume are necessary for the development of parenchymatous keratitis of congenital lues can be produced experimentally. Injection of antihistaminics and local application of cortisone conspicuously restrain the ana-

phylactic reaction of the corneal tissue. (16 figures, 1 table, 75 references)

F. H. Haessler.

3

VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Auricchio, Giacinto. **Independence of the steady-state aqueous-plasma osmotic gradient of the plasma concentration.** Acta ophth. **37**:576-582, 1959.

The blood plasma of nephrectomized rabbits was made hypertonic by the injection of substances (sucrose and naphthalene-2:7 disulphonate), that have a very low steady-state aqueous-plasma ratio. The osmotic gradient between aqueous and plasma recovers in the steady state. This phenomenon is consistent with the assumption that the membrane separating the aqueous from the plasma has such permeability properties that the two solutions are in virtual osmotic equilibrium in spite of the difference in their vapour pressure. (3 tables, 8 references)

John J. Stern.

de Berardinis, E. **The presence of a direct oxidative cycle in the retina.** Ophthalmologica **138**:419-422, Dec., 1959.

In fresh cattle retinas the author has demonstrated the two enzymes, glucose-6-phosphate dehydrogenase and 6-phosphogluconic dehydrogenase, which are involved in the first step of direct glucose oxidation via the hexose-monophosphate shunt. In some but certainly not all layers of the retina the direct oxidative cycle may be the dominant metabolic process. (2 figures, 10 references)

Peter C. Kronfeld.

Boberg-Ans, J., Grove-Rasmussen, K. V. and Hammerlund, E. R. **Buffering technique for obtaining increased physiological response from alkaloidal eye-drops.** Brit. J. Ophth. **43**:670-675, Nov., 1959.

The physiologic action of any alkaloid instilled into the eye results from the penetration through the cornea of the free base of the drug rather than of its ionic form. Because the pH of the eye is 7.4, larger concentrations of the drug must be used to obtain necessary action than if the pH were much lower. It was determined that if the pH of the eye can be changed for the instillation, then considerably weaker solutions could be used with the same functional result. In this study, this was accomplished by first buffering the eye with one or two drops of sterile isontonic sodium borate solution, pH 9.2, and then following this with a single drop of the desired drug salt made isotonic with sodium chloride. Six alkaloid drugs were tested in one eye and the fellow eye was used as an unbuffered control. In the buffered eye a weak solution of one-half to one-twentieth of the concentration usually used gave an equally strong physiologic effect. (12 references)

Morris Kaplan.

Carapancea, M. **Physiopathologic study of ocular disease due to quinine intoxication.** Arch. d'opht. **19**:841-849, Dec., 1959.

The author notes that confusion concerning the mode of action of quinine on the eye in quinine intoxication is due largely to the rarity of cases. He mentions that only five cases were studied in 21 years at the Coltea Hospital. He describes the clinical features of quinine intoxication with particular reference to visual field changes but includes such other signs and symptoms as hemeralopia, paresis of accommodation, visual hallucination, and metamorphopsia. The constant and pathognomonic objective signs of the toxicity include mydriasis, retinal pallor due to edema or to constriction of arterioles, modifications of color and contour of the papilla, and contrasting redness of the macula. He reports the case of a girl of 16 years poisoned by five grams of quinine bisulfate in whom am-

aurosis developed within several hours. He concludes that the primary lesion is intraretinal and not ophthalmoscopically visible, whereas the late lesion is vascular and thus readily demonstrable with the ophthalmoscope. In a study on rabbits he was able to show that retinal degeneration involved the ganglion cells and the rods and cones. He concludes with a discussion of the pathogenesis of the various neurologic signs and symptoms of the intoxication which he believes are due to toxic action on the central nerve centers and on the adrenalin-producing portion of the adrenal gland. (6 references) P. Thygeson.

Cavka, V. **The fronto-orbital centers for intraocular and blood pressure regulation: further investigations.** Ophthalmologica **138**:413-418, Dec., 1959.

After electric stimulation, by a previously described technique (cfr. Am. J. Ophth. 45:883, 1958), of certain cortical areas in the frontal lobes of dogs the author has observed fluctuations in blood pressure and intraocular pressure which he interprets as evidence for pressure-regulating centers. (6 figures, 9 references) Peter C. Kronfeld.

Geeraits, W. J., Chan, G. and Guerry, D. **The effect of alpha-chymotrypsin on zonular and anterior hyaloid membrane: experiments on eyes in the human, rabbit and dog.** South. M. J. **53**:82-85; Jan., 1960.

The authors describe a technique for demonstrating, under direct observation with the slitlamp biomicroscope, the action of alpha-chymotrypsin on the zonular fibers in rabbit eyes in vivo and in dog eyes in vitro. It was observed that a number of zonular fibers were completely dissolved, while others remained identifiable, though structurally modified. They mention that the incomplete lytic action might have been due to rapid inactivation of the enzyme after its injection into the anterior chamber. No effect on the hyaloid membrane was observed after prolonged applications of 1 : 1000 solution of alpha-chymotrypsin to this structure. (8 figures, 7 references) Joseph H. Derivaux.

Huggert, A. **Studies of the water of the crystalline lens. IV. The sodium space of the rabbit lens, measured in vivo.** Acta ophth. **37**:522-527, 1959.

The extracellular space of the cortex and the nucleus of the rabbit lens, measured in vivo by Na^{24}, was found to be 10 to 12 percent and 4 to 7 percent respectively. The superficial parts of the lens showed a higher uptake than did the whole cortex, especially above three years of age. Values for the central parts were rather constant, 3 to 4 percent for all ages. (1 figure, 11 references) John J. Stern.

Krueger, R. and Küchle, N. J. with the collaboration of Böckenhof, W. **The free amino acids and peptids in the lens of pigs and cattle.** Arch f. Ophth. **161**:381-386, 1959.

The authors used Van Slyke's ninhydrin method to determine the amino-nitrogen content of the free amino acids in 69 normal lenses of pigs and 13 of cattle. They found an average of 25 mg. percent. From these data one can calculate that the lens of these animals contains 250 mg. percent of free amino acid. Further scouting measurements suggest that a similar quantity of aminonitrogen of the protein-free lens fluid occurs combined with peptids. (2 tables, 14 references) F. H. Haessler.

Krueger, R. and Küchle, H. J. with collaboration of Kalfhaus, G. **The free aminoacids and peptids in the vitreous of pigs and cattle.** Arch. f. Ophth. **161**:387-390, 1959.

A study similar to the one abstracted above showed that in the vitreous fluid of these animals the average total content of

free amino acids is about 30 mg. percent (2.84 mg. percent amino nitrogen in the pig, 2.99 in cattle) whereas the part played by aminonitrogen in the formation of peptids is essentially smaller. (2 tables, 9 references) F. H. Haessler.

Oksala, A. and Lehtinen, A. **Flourescence analysis of the framework in the congealed vitreous.** Acta ophth. **37**:552-559, 1959.

After injection of sodium fluorescein into the vitreous, ox eyes were frozen with carbon dioxide ice. Examination in ultraviolet light showed the staining substance more strongly attached to the fibers of the vitreous; they formed a net-like framework of uniform density. The vitreous was adhering, in addition to its base, to the equator, the optic dic and the macula. Occasionally it adhered also to the retina at other sites, or to the posterior lens capsule. (4 figures, 40 references) John J. Stern.

Papanos, G., Spitzky, K. H. and Trichtel, F. **The permeation of penicillin into the rabbit's eye.** Arch. f. Ophth. **161**:329-333, 1959.

A water-soluble penicillin was given to rabbits intravenously through an ear vein, intramuscularly in the gluteous musculature or subconjunctivally. Four animals were used for each route. One hour later blood was taken from a vein in the other ear and by puncture of the anterior chamber 0.25 ml. of aqueous was aspirated. When the penicillin had been given subconjunctivally the aqueous was always taken from the same eye. The samples were tested against Staphylococcus aureous in comparison with penicillin V and penicillin G by a modification of the procedure of Dornbush and Pelcak. The aqueous content was greater after the administration of penicillin G than after penicillin V and coresponded to about 1/10 of the serum level after parenteral administration. After subconjunctival application, the serum level was about 1/10 that of the aqueous content. (4 tables, 17 references) F. H. Haessler.

Pedler, C. **Studies on developing retinal vessels. VII. Fluoride-induced vaso-obliteration and its relation to retinal maturity.** Brit. J. Ophth. **43**:681-685, Nov., 1959.

Much work has been done to explain the mechanisms involved in vaso-oblteration in the immature retina in the presence of hyperoxia. Certain experiments have indicated that intravitreal administration of inhibitors of glycolysis, such as sodium fluoride, can bring about this obliteration of vessels in a repeatable manner by retinal swelling which actually mechanically closes off the vessels. Pedler reports the results of these experiments and also a determination of whether there is any similarity between the age at which fluoride ceases to affect the retinal vessels and the age at which hyperoxia becomes ineffective. Injections were made into the vitreous and the drug deposited upon the surface of the retina in the experimental animals. Obliteration of the vessels did occur and this process could be reversed by the injection of 1-percent amethocaine solution. This reaction was consistent up to the age of 14 days after which it became inconstant until 21 days and was completely ineffective after 50 days. These ages are consistent with the changes brought about by ambient hyperoxia. (7 references) Morris Kaplan.

Rohen, J. W. **The resistance to aqueous outflow.** Ophthalmologica **139**:1-10, Jan., 1960.

Previous morphologic studies of the outflow channels in the human eye (cfr. Am. J. Ophth. 48:204, 1959) have been continued and expanded. Tangential sections through the trabecular region show

that the connective tissue fibers increase in fineness and density as the inner wall of the canal is approached. Flocks' pore tissue is a net of argyrophilic fibers surrounding actual holes or pores. There is a complete endothelial lining of the inner wall of the canal, but the individual cells are capable of contraction and deformation "so as to make room for a migrating cell." Perfusion of enucleated human or monkey eyes causes characteristic changes in the inner wall of the canal including the endothelium.

Trephine buttons of early glaucomas show three types of changes: 1. nodular proliferation of meshwork cells. 2. degeneration of the inner wall of the canal with thickening of the pore area, and 3. hyalinization of the membranous coat of the trabeculae.

Summing up, the author believes the principal site of the resistance to aqueous outflow to be located in the inner wall of the canal. There an "endothelium-basement membrane system" actively regulates the rate of aqueous outflow. (12 figures, 22 references) Peter C. Kronfeld.

Sartori, C. **Evaluation of a new vasoconstricting drug in ophthalmology.** Klin. Monatsbl. f. Augenh. **136**:237-240, 1960.

Otriven (Ciba) is a drug derived from Privine hydrochloride. The derivative is mildly astringent and vasoconstricting without causing secondary hyperemia. A 0.1-percent solution was found to be most effective in many nonspecific lesions of the conjunctiva. (1 table, 6 references)

Gunter K. von Noorden.

Semenovskaya, E., Zaretskaya, R., Bogoslovsky, A. and Idanoff, V. **Methods and results of electrophysiological investigations in ophthalmology.** Ophthalmologica **139**:24-44, Jan., 1960.

This report comes from the laboratory for physiological optics (named after S. V. Kravkov) of the Ophthalmological Institute in Moskow named after Helmholtz. In the study of various ocular diseases the investigators employ not only electroretinography (ERG) combined with electroencephalography (EEG) but also determinations of the retinal threshold for single and rhythmic galvanic stimuli. The frequency of intermittent or repeated electric stimuli at which the phosphene disappears can apparently be determined with similar accuracy and consistency as the critical fusion frequency and is therefore named the critical frequency of extinction of the phosphene. This frequency is considered an indicator of the speed of propagation of impulses in the entire visual system and a measure of the state of "relative lability" of brain cells.

The American reader will be particularly interested to learn that in glaucoma the threshold for single galvanic stimuli is within normal limits while the critical frequency of extinction of the phosphene is markedly lowered.

The Russian investigators have paid special attention to abnormalities in the electroencephalogram in glaucoma and have reached the conclusion that the glaucomatous pathologic process may affect higher visual centers before it affects the retina.

Electrophysiologic methods may also be of investigative value in diseases such as concommitant strabismus, retinal detachment and retinitis pigmentosa. (10 figures, about 50 references)

Peter C. Kronfeld.

Steinvorth, E. **Experimental study of the behavior in electrophoresis of water-soluble proteins of the corneal epithelium of the calf under the influence of various temperatures and medicaments.** Arch. f. Ophth. **161**:466-491, 1960.

The author investigated the effects of eight groups of medicaments, namely: astringents, chemotherapeutic and anti-

biotic agents, local anesthetics, vasoconstrictors, vasodilators and lymphogogues, epithelial regenerators, miotics, and mydriatics. (13 figures, 1 table, 45 references)
F. H. Haessler.

Trichtel, F. and Papapanos, G. **Comparative corticosteroid determinations in the normal aqueous of various mammals.** Arch. f. Ophth. **161**:325-328, 1959.

By means of the modification of the tertazol-blue test of Mader and Buck, differences were determined in the corticosteroid content of the aqueous of mammals of the same and different species. Though great variation of concentrations were found among the various genera, differences within a genus were insignificant. The authors also showed that the corticosteroid content of the aqueous is greater in older animals than in the younger. (1 figure, 1 table, 10 references)
F. H. Haessler.

Vesey, F. A. **Effects of mechanical obstruction of the chamber angle in rabbit eyes.** Ophthalmologica **139**:11-19, Jan., 1960.

To decide the importance of the structures of the chamber angle in the generation of increased intraocular pressure, various methods were tried to obstruct the angle in the rabbit. The results of implantation of a circling polyethylene tube into the angle are now reported in detail. Tubes of 0.6 to 0.9 mm. outside width were bent to a U-shape and introduced through a small corneal incision into the anterior chamber where they adapted themselves perfectly to the shape of the angle. A remarkable phenomenon occurred two to three days after the operation: a ring-like, 2 to 3 mm.-wide, bright red peripheral zone of corneal vascularization developed, lasting two to three weeks and leaving the central part of the cornea perfectly clear. The eyes with implants were observed clinically for a number of months. The constant clinical finding was a decrease of the intraocular (tonometric) tension in the eye operated upon to half of normal or less.

At various intervals an animal was killed and the eye operated upon examined histologically. The free ends of the tube slowly pressed themselves into the spongy tissue between ciliary body and sclera, gradually progressing into and to the rear of the ciliary body. The muscle and connective tissue of the ciliary body formed a wall around the tube and the spongy tissue of the angle seemed to return to normal.

The author states that the permanent lowering of pressure in the eye operated upon could have been only due to one factor, namely decreased formation of aqueous. Nevertheless he believes that "these experiments create a powerful argument against the theory that any sort of obstruction or blocking in the spongy tissue of the chamber angle in the canal of Schlemm would result in increased intraocular pressure followed by other pathologic changes named glaucoma." (5 figures) Peter C. Kronfeld.

de Vincentiis, M. and Testa, M. **Researches for biochemic characterizing of the phosphomono-esterase of ocular tissues.** Acta ophth. **37**:491-494, 1959.

There is a biological analogy between the phosphomono-esterase of choroid and corneal epithelium, and the osseous phosphomono-esterase; no such analogy was found for the corresponding enzyme of the retina. This is interesting because of the fact that only choroid and cornea can undergo osseous metaplasia. (1 figure, 7 references) John J. Stern.

Walters, P. T. **Anaerobic glycolysis in rats affected with retinitis pigmentosa.** Brit. J. Ophth. **43**:686-696, Nov., 1959.

Retinitis pigmentosa is a hereditary disease of unknown etiology character-

ized by a progressive course beginning in childhood with night-blindness and progressing to severe retinal pigment changes which frequently lead to blindness. Pathologically there is a degeneration of the retinal neuro-epithelium, particularly of the rod cells, with attenuation of the retinal blood vessels and optic atrophy. A closely similar condition which is also hereditary occurs in rats and presents the same pathologic features. Walters believes that studies of the metabolism of the retinas of these rats might lead to some understanding of the disease in man and to this end investigation of the anaerobic glycolysis of the retina, which is extremely high in the rat, was carried out.

The rats were first bred to a pure line of diseased animals, which took several generations, and then the rate of anaerobic glycosis was measured by a manometer. It was found that this metabolic process presented a rate of about 18 percent lower in the affected retinas than in normal animals and this was found to be so at an age prior to appearance of histologic changes. This lowered metabolism may well be due to the absence of a particular enzyme.

In the rabbit it has been found that intravenous injections of sodium iodoacetate could produce retinal lesions very similar to those of retinitis pigmentosa and in these animals a lowered rate of anaerobic glycolysis was also found. These results indicate that in the rat, at least, the disease is most probably a metabolic disturbance rather than a progressive retrogression or abiotrophy. (24 figures) Morris Kaplan.

4
PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

ten Doeschate, G. **Cezanne, a forerunner of Luneburg.** Ophthalmologica **138**: 456-458, Dec., 1959.

Luneburg is the author of a mathematical analysis of the subjective visual space (Princeton 1947) which Linksz presented in abridged form in his Physiology of the Eye.

Some of Cezanne's paintings were used for the analysis of subjective space because actual photographs of some of the landscape subjects were available. The photographs clearly showed that Cezanne had painted the background objects relatively larger (compared to the foreground), apparently to satisfy his own subjective visual space. This relative enlargement of the background is one of the principal features of Luneburg's geometric analysis.

ten Doeschate's point of view is that Cezanne had possibly recognized the weakness, in terms of space values, of photographs of a landscape and had instinctively or intentionally corrected it by making his background objects exceed their actual visual angles. (2 figures, 6 references) Peter C. Kronfeld.

Laterza, A. **Egocentric localization of objects in space as a non-exteroceptive function.** Riv. oto-neuro-oftal. **34**:181-192, March-April, 1959.

The egocentric localization of objects in space can be either exteroceptive (a retinal-foveal function) or non-exteroceptive. The author reviews the literature concerning the non-exteroceptive mechanism and presents personal observations of errors in localization which were observed as a result of an ophthalmoplegia. (25 references) Wm. C. Caccamise.

Lima, F. **After-image studies.** Rev. brasil. oftal. **18**:293-304, 1959.

The author studies after-images and after his analysis of the entire phenomenon he chooses Cueppers' concept of the after-image. Through the interpolation of prisms, he demonstrates that the after-image is not a real image but a spatial

perception. The author produces Cueppers' after-image and transfers it to the opposite eye from the one to be stimulated and feels that this will be of great significance in the treatment of amblyopia. (4 figures) Walter Mayer.

Martins, M. **Treatment of amblyopia.** Rev. brasil. oftal. **18**:335-341, Dec., 1959.

The author outlines the treatment of amblyopia according to the ideas of Cueppers and he summarizes the results he obtained in 28 cases. (5 references) Walter Mayer.

Oppel, O. and Schmidt-Mumm, E. **The functional aspects of amblyopia and its relation to phylogenesis.** Arch. Soc. oftal. hispano-am. **19**:805-814, Oct., 1959.

The authors review briefly the development of the visual function in lower animals and discuss in greater detail the development of the visual functions in man. The function of the hypothalamus, of the anterior quadrigeminal bodies and of the external geniculate bodies is described and illustrated. Reference is made to the work of Harms and Granit on the centrifugal conductibility of the optic nerves and pathways. In amblyopia the most primitive function is not affected. The perception of light and dark functions in the most severe cases of amblyopia. The disturbances involve the latest philogenetic function which is the orthognostic ability; it may vary from but a slight to a complete loss. Along with the loss of central visual acuity may be associated other orthognostic disturbances such as incapacity of definition, eccentric fixation, difficulty of localization and oculomotor disturbances. The most severe amblyopia has a visual acuity equal to that of an infant six to eight weeks old, in whom the recognition of objects has not as yet developed. Pediatricians should be informed that the success of the treatment of amblyopia is in direct relation to the time at which the treatment is instituted. (4 figures) Ray K. Daily.

Pimentel, P. **Asthenopia.** Rev. brasil. oftal. **19**:5-10, March, 1960.

The author feels that glasses are very often not the only answer to a problem of asthenopia. Emmetropia and orthophoria are the exception rather than the rule but some refractive errors do not require correction. For example, a hyperopia of 0.75 diopters in small children does not require correction. Phorias, convergence and accommodation have to be checked in cases of asthenopia. Walter Mayer.

Warburg, M. **Occupational prognosis in excessive myopia. Illustrated by a series of patients from the State Institute for the Blind and weak-sighted.** Acta ophth. **37**:467-490, 1959.

Review of 74 persons, blind as well as weak-sighted as a result of excessive myopia, encourages a very optimistic view concerning their vocational guidance. Especially the young patients have been able to pursue other than the "traditional blind persons' trades." However, once they are rendered useless on the labor market, their chances of rehabilitation are scarcely better than those of persons with acquired blindness. (9 tables, 8 references) John J. Stern.

5
DIAGNOSIS AND THERAPY

Brodsky, M. and Brodsky, M. E. **Results obtained with the after-image method in the treatment of amblyopia.** Arch. oftal. Buenos Aires **34**:279-283, Nov., 1959.

After giving a brief outline of the treatment of amblyopia as advocated by Cüppers, the authors report the results obtained in 40, mostly strabismic, amblyopic patients ranging in age from five to 28 years. These patients were among un-

specified numbers with central fixation which did not respond to occlusion of the sound eye, with unstable central fixation, with eccentric fixation, and, lastly, with a wandering, indefinite type of fixation. In 10 patients no amelioration took place, in 23, only a moderate gain (from 0.1 to 0.4) could be obtained, in three, a marked improvement (of an order of 0.7 to 0.9) was achieved, while in none was the 20/20 level reached. The best results were obtained where fixation was central, though occasionally unstable; when it was eccentric, on the other hand, the results were of little practical consequence. (1 table)

A. Urrets-Zavalía, Jr.

Enrico, L. and Rogers, A. **Beta therapy in ophthalmology.** Rev. brasil. oftal. **18**: 311-332, Dec., 1959.

The authors give a rather complete summary of the physical and physiological characteristics of beta-ray therapy and then outline the indications, contraindications and restrictions to this form of therapy. Their experience with this form of therapy in 64 patients is tabulated. (3 figures, 3 tables, 18 references)

Walter Mayer.

François, J. **Photocoagulation in ophthalmology.** Ann. d'ocul. **193**:1-16, Jan., 1960.

The author reviews the indications for the use of the photocoagulator and illustrates his article with pre- and post-operative fundus photographs. These include macular holes without detachment, peripheral tears without detachment, retinal periphlebitis, choroidal sarcomas, metastatic carcinomas of the choroid, angiomata and retinoblastomas.

In the case of tumors, successful photocoagulation is possible only in sharply circumscribed lesions of small size. Approximate figures are given for these. (17 figures, 5 references) David Shoch.

Krasnor, M. L. and Borishpoletz, V. I. **The problems of anesthesia and potentiated premedication of surgical patients in ophthalmology.** Vestnik Oftal. **3**:3-10, May-June, 1959.

The authors emphasize their use of premedication in eye surgery where local anesthesia is employed. They administer bromides for several days prior to surgery, phenobarbital in doses of 100 mg. the night before operation and 100 mg. of phenobarbital or nembutal one hour before operation. In addition they administer one hour before surgery a mixture consisting of 25 to 50 mg. of aminasin (a tranquilizer), 20 mg. dimedrol (for its anti-histaminic effect), and 10 mg. of promedol (an analgesic). They have noted a marked improvement in the attitude of the patient as well as a diminution in operative and postoperative complications. (62 references)

Victor Goodside.

Mackay, R. S., and Marg, E. **Fast, automatic, electronic tonometers based on an exact theory.** Acta ophth. **37**:495-507, 1959.

If a powder conducting electricity is mixed with a binder that retains some flexibility on drying, a paint is obtained which changes its electrical resistance with pressure. Increasing force compresses the material slightly and causes a decrease in resistance to be indicated by an ohm-meter. This principle has been used to construct a tonometer in which a dried dot of such paint is pressed against the cornea and the change of its electrical resistance is used to measure the intraocular pressure. In a second application of the same principle the flattening of the cornea under pressure from the instrument is used to estimate the ocular tension. In a third, and preferred alternative, pressure of the instrument flattens the cornea beyond the area of the pressure-sensitive paint and it is shown that with

this method the only force applied to the paint transducer is that of the intraocular pressure. Another principle is presented in which a minute crystal oscillator is used as transducer. In still another form a metal plate covered with a limp, conducting diaphragm is pushed against the eye. The electric capacity between the diaphragm and a metallic back plate can be measured by a suitable capacity detector. Finally a motion sensor can be employed in which the motion of a small plunger is sensed by a coil which detects the displacement of a ferrite core. Technical details are presented which should be consulted in the original article. It is not quite clear whether all these instruments have actually been built, but one, at least, the one using a motion sensor, has been tested and compared with the Mueller, Schiøtz, and Goldmann tonometer. It is claimed that it is not significantly affected by corneal elasticity or rigidity, corneal curvature or astigmatism, or surface tension of lacrimal fluid. No auxiliary devices, such as slitlamps or corneal microscopes are necessary and no complicated calibrations required. The instruments promise to be sufficiently simple and inexpensive to allow their use not only by optometrists and ophthalmologists but also as screening devices by the general practitioner. (8 figures, 6 references)

John J. Stern.

Mikuni, M., Yoneyama, T., Ishii, K. and Makabe, R. **Optical transposition of measurements on the fundus.** Klin. Monatsbl. f. Augenh. **136**:161-166, 1960.

Measurements are made with a measuring ocular (after Mikuni) in a Gullstrand ophthalmoscope. The total refractive power of the eye, which varies considerably, is an important constant in the transposition of instrument readings into absolute values. The optical measurements of the optic disc were compared with actual anatomical measurements in enucleated eyes and the total refractive power of the eye was calculated by means of a formula. An average value of 66.6 D was obtained, but deviations as great as 10 D were observed. (4 tables, 14 references)

Gunter K. von Noorden.

Moreno Cadierno, M. and Crespi Carcar, F. **Treatment of ocular burns with Vasculat.** Arch. Soc. oftal. hispano-am. **19**:815-818, Oct., 1959.

Vasculat, suggested for the therapy of ocular burns by Leydecker, is chemically a p-oxyfenil-etanol-butilamin. It is a derivative of sympatol, with distinct pharmacologic characteristics. It is a vasodilator and exerts its action on the arteries and especially on the capillary segment. The author reports four cases, two of severe acid burns of the anterior ocular segment, one of traumatic bullous keratitis, and one of non-traumatic keratitis, in which the patient recovered promptly under instillations of Vasculat.

Ray K. Daily.

Pillat, A., Trichtel, F. and Oberhummer, M. **Fundamental data for iodine therapy of the eye.** Arch. f. Ophth. **161**: 319-324, 1959.

The authors used the very sensitive micromethod of Spitzy, Reese and Skrube for the first measurements of the iodine content of the aqueous and the tissues of the eye and their relation to the iodine content of the serum. The eyes of man, cattle and rabbits were used. Because the quantity of iodine is small in all of the tissues except the sclera it was necessary to use a sample of at least 200 mg. of moist tissue. In order to get samples of this size of some of the tissues several eyes had to be pooled. The iodine content of the lens is less than 0.4 μg percent and in the vitreous it varied between 0.2 and 1.2 μg percent. In tissue with an active circulation, the anterior uvea and the choroid for ex-

ample, the iodine content depends on the iodine level in the aqueous and the serum. In the sclera the iodine level was surprisingly high in every case. The iodine level in the aqueous is between 1.2 and 7.0 μg percent and its average is 10 to 20 percent lower than in the blood serum, where is varied between 1.7 and 7.2 μg-percent in man, cattle and rabbits. In the sclera the iodine content varied between 5.6 and 16 μg percent and is probably due to the small moisture content of this tissue. In the lens and the vitreous no iodine was demonstrable in almost all of the eyes. (3 tables, 10 references)

F. H. Haessler.

Rossi, G., Canossi, G. C. and Pasquinelli, C. **The diagnostic use and possible therapeutic effects of cerebral pneumography in opticochiasmatic arachnoiditis.** Riv. oto-neuro-oftal. **33**:611-653, Nov.-Dec., 1958.

Studies by the authors indicate that air cisternography can be of both diagnostic and therapeutic importance in patients with opticochiasmatic arachnoiditis. In some patients with negative cisternoencephalographic findings a beneficial therapeutic effect appeared to substantiate a diagnosis of the underlying inflammatory process. (6 figures, 12 diagrams, 25 references) Wm. C. Caccamise.

Santalices Muniz, F. **A new model of an anterior chamber canula.** Arch. Soc. oftal. hispano-am. **19**:819-821. Oct., 1959.

This anterior chamber irrigating needle is shaped like a cyclodialysis spatula and has two openings laterally, one on each side close to its blunt end. The advantage claimed for it is the elimination of the danger of injury to the corneal endothelium or the lens capsule by a stream which is directed forward or backward. (2 figures) Ray K. Daily.

Tokareva, B. A. **Combined method of anesthesia in ophthalmic surgery in children.** Vestnik Oftal. **3**:16-22, May-June, 1959.

The author describes a system of anesthesia used with satisfaction in 800 eye operations on children.

A cleansing enema was given at 7 A.M. and a light breakfast at 9 A.M. One hour before operation phenobarbital was given, and directly before going to the operating room the child was given a two-percent chloral hydrate solution rectally. On the operating table a subcutaneous injection of promedole (an analgesic) was followed by a retrobulbar injection of two-percent novocaine and a topical anesthetic by instillation. A superior rectus suture was placed. In older children an intramuscular injection of dimedrol (an antihistaminic) was also administered one hour before operation. The doses used naturally varied with the age, general condition of the child, his mental make-up, and the character and duration of the operation. (2 tables, 13 references) Victor Goodside.

6 · OCULAR MOTILITY

Adams, Alfred. **The duration of optokinetic excitation. A contribution to "A study of the physiology of the optokinetic afternystagmus" by Mackenson and Wiegmann.** (Arch. f. Ophth. 160:497-509), Arch. f. Ophth. **161**:334-340, 1959.

Adams' study of the afternystagmus, which appears with the eyes closed after preceding optokinetic nystagmus, is based on the analysis of 72 electronystagmograms (ENG) and 11 pathologic ENG. This "optokinetic afternystagmus" was always horizontal, after vertical as well as horizontal movement of the stimulating pattern. It was however much more frequent after horizontal movement. Reasons are brought forth for not accepting the rotating strip of light which served as "stimulating pattern" as a specific stimulus

for releasing the optokinetic afternystagmus. The optokinetic afternystagmus is probably the result of a thalamo-reticular persistence of stimulus. Pathologic distribution of opto-vestibular fundamental stimulation will either be chanelled or inhibited. (2 figures, 2 tables 6 references)

F. H. Haessler.

Arruga, A. **Early squint surgery and anomalous correspondence.** Rev. brasil. oftal. **18**:285-291, Dec., 1959.

The author feels that surgery in the very young patient is contraindicated because an exact examination is not possible. While a fairly good cosmetic result may be obtained it is, however, possible to leave uncorrected very small amounts of deviation, especially vertical deviation, which, due to their small size, are much harder to correct later on. Unless the squint is extremely large, surgery should be postponed until the child is somewhat older.

Walter Mayer.

Bagonini, B. and Tavolara, L. **A clinical study of the development of amblyopia in cases of concomitant strabismus.** Boll. d'ocul. **38**:102-114, 1959.

The authors conclude that suppression scotoma does not always develop in cases of concomitant strabismus. They found that the greater the angle of strabismus, the more likely was suppression to develop, whereas in cases of small-angle strabismus suppression was not invariable. Patients who had small-angle strabismus, could perceive diplopia and had normal retinal correspondence were less likely to develop suppression and amblyopia. The ability to fuse made the development of suppression phenomena less likely. (2 figures, 1 table, 22 references)

Joseph E. Alfano.

Lian, O. K. **Muscle transplantation as additional therapy in concomitant strabismus.** Ophthalmologica **138**:431-435, Dec., 1959.

In five cases of concomitant and in one case of paralytic esotropia extensive surgery on the horizontal recti resulted in only partial correction of the deformity. Additional tendon transplants after Hummelsheim actually reduced the deviation and contributed substantially toward a satisfactory cosmetic result. (23 figures)

Peter C. Kronfeld.

Mariotti, L., and Zucchi, M. **A relationship between concomitant strabismus and anomalies of behavior in the infant.** Riv. oto-neuro-oftal. **33**:685-698, Nov.-Dec., 1958.

X-ray examination of the skull in 24 children with nonparalytic strabismus revealed slight changes or variations from the absolutely normal that might possibly suggest a relationship between the strabismus and a previous cerebropathy. (3 figures, 6 references)

Wm. C. Caccamise.

Martins, M. **A case of paralysis of the internal rectus.** Rev. brasil. oftal. **19**:39-43, March, 1960.

The author presents a case of paralysis of the medial rectus muscle which was corrected surgically by cutting the insertion of the superior oblique muscle and transplanting it into the medial rectus insertion and then recessing the lateral rectus muscle. (6 figures)

Walter Mayer.

Naylor, E. J. and Stanworth, A. **Binocular depth perception in small-angle strabismus.** Brit. J. Ophth. **43**:662-669, Nov., 1959.

Despite apparent good functional results in strabismus which has had treatment, depth perception is often found to be quite poor. On a new modified major amblyoscope it is possible to measure

and study small-angle squints and this was done in the patients described in this paper in an attempt to explain the poor depth perception. The determination of depth perception in the young patient is very difficult and requires some compromise; it was done here in 66 patients using two vertical rods with one being movable forward and backward. It was found that there is a definite relationship between the difficulties of depth perception and derivations from parallelism even to less than 0.5 prism diopter. Those patients who had abnormal retinal correspondence also presented the greatest disparity in depth perception. (6 references)

Morris Kaplan.

Pirodda, A. and Cenacchi, V. **Electronystagmographic studies of a case of acute concomitant strabismus.** Riv. oto-neuro-oftal. **34**:500-521, Sept.-Oct., 1959.

The authors state that acute concomitant stribismus is a relatively rare condition which has as its fundamental clinical characteristic a rather abrupt onset which is accompanied by diplopia and a predilection for adult patients. They present in detail their findings in a 16-year-old girl. (3 figures, 40 references)

Wm. C. Caccamise.

Sachsenweger, R. **The photographic measurement of the apparent angle of squint.** Arch. f. Ophth. **161**:391-398, 1959.

The patient fixates the point of crossing of two threads at right angles in the objective of the camera. During the exposure a cross-lined design in the circular flash of the camera is reflected from the cornea and shows the position of the point of penetration of the line of sight in the cornea. From the distance of this point from the center of the cornea the angle gamma can be calculated. The author analyzes the possibilities of error. (6 figures, 1 table, 7 references)

F. H. Haessler.

Scassellati Sforzolini, G. **A very rare syndrome: unilateral congenital defect of elevation with retraction of the globe.** Riv. oto-neuro-oftal. **33**:431-439, July-Aug., 1958.

The author presents the findings in a 25-year-old woman with an unusual type of congenital anomaly of the external ocular muscles. There was a marked deficiency in the left superior rectus muscle together with slight underaction of the homolateral inferior rectus muscle. In addition, a very definite anophthalmos was noted. Surgical exploration revealed that the superior rectus muscle was split into two bundles which were inserted at two different sites in the sclera. (3 figures, 8 references)

Wm. C. Caccamise.

7
CONJUNCTIVA, CORNEA, SCLERA

Alfonso, G. F. and Boeri, R. **A case of oculo-facial melanosis.** Riv. oto-neuro-oftal. **33**:303-308, May-June, 1958.

The authors describe and discuss a case of oculofacial melanosis in a 25-year-old woman. The patient first became aware of scleral pigmentation in the left eye at the age of 21 years. There was a progressive increase in the pigmentation. In association with pigmentation of the skin of the left lids and left temporal region, there was a trigeminal neuralgia involving the first division of that nerve. Possible etiological bases for this type of melanosis are discussed. (5 figures, 12 references)

Wm. C. Caccamise.

Franceschetti, A. and Forgacs, J. **Histologic findings in a case of white limbus girdle.** Ophthalmologica **138**:393-398, Dec., 1959.

An eye with the typical white limbus girdle of Vogt became available for histological examination because of coincidental absolute glaucoma. The findings were very similar to those in primary

band-shaped corneal dystrophy. A close relationship between the two conditions is assumed. (2 figures, 18 references)

Peter C. Kronfeld.

François, J. and de Rouck, A. **Electroretinographic and electroencephalographic findings in Hurler's disease.** Ophthalmologica **139**:45-55, Jan., 1960.

Four typical cases of Hurler's disease, in two brothers from each of two families (A and B) are reported. In family A the children were three and five years of age, respectively; they showed the typical corneal dystrophy and normal eyegrounds. The electroretinograms were also normal. In family B the affected individuals were 13 and 16 years of age, respectively; the corneal dystrophy was so extensive that the eyegrounds could not be seen. The electroretinograms were practically extinguished and the dark adaptation was delayed. The findings are interpreted as signs of a tapeto-retinal degeneration. "Hurler's disease can be classified among the large group of heredo-degenerative, cerebro-retinal affections depending essentially on disorders of the lipid and protein metabolism. (4 figures, 41 references)

Peter C. Kronfeld.

Hobbs, H. E. and Calnan, C. D. **Visual disturbances with antimalarial drugs, with particular reference to chloroquine keratopathy.** A.M.A. Derm. **80**:557-563, Nov., 1959.

A large portion of patients under treatment with oral chloroquine for lupus erythematosus show deposits of an opaque substance in the corneal epithelium. Visual acuity is ordinarily not affected but there are various complaints of visual disturbance, particularly of halos around lights. The slitlamp shows fine white dots and often they are arranged in a subpupillary line resembling the Hudson-Stähli line characteristic of long-standing ocular disease. These opacities may appear as early as three weeks after beginning treatment with chloroquine and usually disappear slowly after stopping the drug. (10 figures, 17 references)

Edward U. Murphy.

Jahnke, W. **Trachoma in Iraq and Afghanistan.** Ophthalmologica **138**:422-430, Dec., 1959.

The author practiced ophthalmology in governmental hospitals in Bagdad, the capital of Iraq, and in Kabul, the capital of Afghanistan. The incidences of trachoma in the two countries, as estimated in "Global Epidemiology" are probably much too low. Practically all the patients seen in eye clinics or in the author's private practice showed signs of trachoma, that is a microscopic pannus or islands of subconjunctival infiltration. Cataract incisions through the pannus usually result in temporary total clouding of the cornea. In cases of severe pannus the author's choice is cataract extraction through the lower limbus. Without any treatment trachoma often runs a mild course but does not subside altogether. Secondary infection leading to severe corneal ulcers is relatively rare.

In mountainous Afghanistan a number of factors militate against effective treatment of trachoma: the small number of physicians, the poor means of transportation, the very sheltered life of all women prescribed by their religion and the nomadic life of a good portion of the population. (2 figures, 6 references)

Peter C. Kronfeld.

Massimeo, A. and Salonna, F. **Cochleovestibular changes in glaucoma.** Riv. otoneuro-oftal. **33**:569-591, Sept.-Oct., 1958.

Cochleo-vestibular studies were made of 34 patients with various types of glaucoma. A perceptive type hearing deficiency which was primarily limited to the higher frequencies was found in 27 of

these patients. Significance, however, is placed on the fact that most of the patients with hearing deficiency were over 50 years of age and showed a degree of impairment of hearing that corresponded to the usual presbyacusia. The exact relationship between the ocular and cochlear changes in glaucoma patients would appear to remain a somewhat unsettled matter. (17 references)

Wm. C. Caccamise.

Mosquera, J. M. and Norbis, A. L. **Scleromalacia in chronic porphyria. Report of a case treated by a lamellar corneal transplant.** Arch. oftal. Buenos Aires **34**:292-299, Nov., 1959.

In addition to scleromalacia perforans vera, scleritis nodularis necroticans, senile hyaline scleral degeneration, and the seldom encountered paralimbic scleromalacia, a special type of scleromalacia in the form of neatly circumscribed atrophic areas of sclera which appear in the horizontal meridian between the limbus and the insertions of the medial and lateral rectus muscles has been observed in cases of chronic prophyria. Only some five well-authenticated cases of this rare condition have been described so far, always in middle-aged male patients. Apart from the above ocular lesions, and from a corneal opacity or the formation of anterior synechias which may occasionally occur, an abnormal sensitivity to light, leading to the appearance of cutaneous lesions known as hydroa vacciniforme and to an ultimate areolar atrophy of the skin, has been reported. A reddish, Portwine discoloration of the urine, due to the excretion of porphyrins, and a marked emaciation, particularly of the face, are also usually present.

The case of a 69-year-old man is reported who had had photophobia for the last five years, and who, on examination, was seen to show all the classical symptoms of the malady. Vision was 20/20 in each eye. As the scleral dehiscence found in the right eye seemed to have a tendency to perforation, a 5 by 7 mm. lamellar scleral autograft was taken from normal territory and sutured into the lesion, from which a thin, bluish-gray, hyaline membrane had previously been removed. The transplant, which at the end of one month became somewhat atrophic, remained otherwise unmodified for the next six months of the follow-up period. Pathologic examination of the affected tissue revealed only the presence of a hyaline material with calcareous deposits. (1 table, 8 references)

A. Urrets-Zavalía, Jr.

Scholtyssek, H. **Late keratitis after mustard gas poisoning. Importance of early diagnosis in regard to therapy and evaluation for compensation.** Klin. Monatsbl. f. Augenh. **136**:243-254, 1960.

Two cases are reported. Marginal ulcers occurred in one patient two years after contact with mustard gas, in another case as late as 19 years after exposure. Early and late symptoms, the course of the disease, as well as its pathogenesis are discussed. Interference with corneal nutrition, aggravated by connective tissue and peripheral nerve damage, are thought to be of pathogenetic significance. Corneal transplantation is recommended. (6 figures, 19 references)

Gunter K. von Noorden.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Battistini, A. and Paganoni, C. **Alterations of pupillary motility in dystrophia myotonica.** Riv. oto-neuro-oftal. **34**:149-167, March-April, 1959.

The authors point out that there is very little discussion in the literature concerning the behavior of the pupil in dystrophia myotonica and that most authors do not describe any particular

change in the iris muscles which, like all smooth muscles, rarely participate in this disease process. The authors then review the characteristics of dystrophia myotonica. Pupillographic studies in two of their own patients are then described. (27 references) Wm. C. Caccamise.

Cambiaggi, A. **Studies pertaining to the possibility of a rheumatic etiology of uveitis.** Boll. d'ocul. **38**:11-25, Jan., 1959.

The author studied 110 cases of established uveitis. In addition to a complete ophthalmologic work-up, the studies included determinations of the anti-streptolisin titer, the C-reactive protein, sedimentation rate, total proteins, albumin-globulin ratio and electrophoretic patterns of the serum proteins. It is concluded from these studies that eight percent of cases had a rheumatic background. (6 tables, 27 references)

Joseph E. Alfano.

Dorello, U. **The eye and the sinuses.** Riv. oto-neuro-oftal. **34**:168-180, March-April, 1959.

In 100 cases of uveitis the author found that 42 of the patients showed changes in the paraorbital sinuses when examined by X-ray. The author believes that such statistics suggest a possible causal relationship between the two conditions. (5 figures, 13 references)

Wm. C. Caccamise.

Liegl, O. **Cytostatic treatment of choroidal metastases with Bayer E 39 (soluble) and 3231. (Development of a bilateral pupillotonia.)** Klin. Monatsbl. f. Augenh. **136**:185-195, 1960.

Liegl reports treatment with a cytostatic drug (ethylene-imino-chinone) in a case of bilateral choroidal metastases from a carcinoma of the breast. X-ray treatment as well as hormonal therapy had failed to reduce systemic and ocular metastazation in this 48-year-old woman. The drug was given repeatedly over a period of two years and resulted during the period of each administration in subjective and objective improvement of the ocular lesions, and regression of systemic metastases. To prevent acute exacerbations of the disease a continuous cytostatic therapy with frequent controls of the white blood count is advisable. An incidental finding was the development of bilateral pupillotonia, presumably due to local damage of the ciliary nerves. (7 figures, 20 references)

Gunter K. von Noorden.

9

GLAUCOMA AND OCULAR TENSION

Draeger, J. and Müller, H. **New viewpoints in evaluation of the water-drinking test.** Klin. Monatsbl. f. Augenh. **136**:203-214, 1960.

The behavior of ocular tension and scleral rigidity was determined during the water-drinking test in 26 glaucomatous and 14 healthy eyes. A significant alteration of the rigidity coefficient was detected and found to be inversely proportional to the behavior of ocular tension. This indicates that measurements obtained with the Schiøtz tonometer alone tend to be too low during the water-drinking test and might actually mask significant increase of ocular tension. Therefore, the use of the applanation tonometer is strongly advised for evaluation of the water-drinking test. (15 references, 8 figures, 5 tables)

Gunter K. von Noorden.

Hoffmann, D. H. **Follow-up examination on 164 eyes after trepanation, with regard to pre-operative treatment with irreversible cholinesterase inhibitors.** Klin. Monatsbl. f. Augenh. **136**:215-218, 1960.

Trephine surgery after Elliot was performed in 164 eyes with chronic simple glaucoma; 84 patients were treated preoperatively with cholinesterase inhibitors

(Mintacol, DFP, Fosmilen), the remaining group received either pilocarpine or no miotics at all. Anterior chamber hemorrhages, as well as a tendency to form posterior synechiae, were observed more frequently in the first group. Vasodilatation and increased capillary permeability are thought to be the direct cause of these complications. The author advises caution in using any of the cholinesterase-inhibiting drops for prolonged periods of time. (21 references, 2 figures)
Gunter K. von Noorden.

Leydhecker, W. **Suggestions for publications on glaucoma surgery.** Klin. Monatsbl. f. Augenh. **136**:219-224, 1960.

During a survey of the literature on glaucoma surgery, the author gained the impression that comparison between published results meets with greatest difficulties. Grouping of the material, evaluation of the results, and length of follow-up period differ from author to author. In order to allow comparison between different reports, the following factors should be considered uniformly in the pre-operative evaluation of glaucoma: appearance of the chamber angle, field defects, number of preceding surgical procedures, and tension prior to surgery. The evaluation of surgical results should include: behavior of tension with and without medication, and function of the eye as expressed in visual field tests. (4 references) Gunter K. von Noorden.

Pompeu C. and de Carvalho, C. **Glaucoma associated with essential iris atrophy.** Rev. brasil. oftal. **19**:55-59, March, 1960.

The authors summarize the generally accepted ideas about the presence of glaucoma in cases of essential iris atrophy and report briefly their findings in a patient. The glaucoma in their patient was controlled by means of cyclodialysis. (1 figure, 10 references) Walter Mayer.

Prijot, E. and Weekers, R. **Deformity of the globe during tonometry.** Arch. d'opht. **19**:825-840, Dec., 1959.

In an exhaustive study of changes in the shape of the globe during tonometry, the authors review the literature on the subject and report experimental studies on pig and human eyes. They were able to establish the following five points from their study: 1. The placing of a tonometer of Schiøtz on a globe produces, in addition to the indentation of the cornea, a deformity localized to the posterior pole. 2. The volume of this posterior deformity during experimental tonometry on removed eyes varies according to the manner in which the globe is supported. 3. Calculation of global rigidity should take account of the total volume displaced by tonometry and not only of the volume of the corneal indentation. 4. The relative importance of the posterior deformity in relation to the corneal indentation is constant, whatever the intraocular pressure. It increases, however, as a function of the weight of the tonometer piston. 5. In the study of the relation between volume and intraocular pressure, it would be desirable to substitute the term "coefficient of capacity" for the term "coefficient of rigidity."

The authors conclude that in the near future it should be possible to substitute a new table of volume of liquid displaced during tonometry, not only as a result of corneal indentation but as a result of posterior pole deformity. (11 figures, 3 tables, 7 references) P. Thygeson.

Tavolara, L. **The action of meprobamates on the intraocular pressure of normal and glaucomatous subjects.** Boll. d' ocul. **38**:11-25, Jan., 1959.

The author studied the action of meprobamate in 75 normal and glaucomatous subjects. The meprobamates did not produce a change in the coefficient of facility of outflow or in the scleral rigidity in

either group. In both groups, however, it produced a significant lowering of the intraocular pressure averaging 3.7 mm. Hg in normal eyes and 8.6 mm. Hg in glaucoma. It was felt that this lowering of the pressure in both groups was due to a diminution in aqueous formation. (4 tables, 37 references)

Joseph E. Alfano.

Valu, L. and Cluelloeg, F. **Gonioscopic observations after Kettesy's cyclodiathermy operation.** Ophthalmologica **139**: 20-24, Jan., 1960.

The aim of Kettesy's cyclodiathermy operation is the obliteration of both long posterior arteries as well as a complete block of the long ciliary nerves. This is accomplished with a high-frequency current applied to the sclera by means of a flat electrode to the point of actual "parching," that is grayish-black discoloration of the sclera. In a number of cases this form of diathermy resulted in undesirable side-effects due to an overdose of current. Corresponding to the area of operation the peripheral iris segments became atrophic; the angle landmarks and the marginal corneal capillary plexus became obliterated. Close observation of the postoperative gonioscopic picture has guided the authors toward a milder form of diathermy (10 to 15 mA for two seconds over an area of 6 × 2 mm. of sclera). (4 figures, 2 references)

Peter C. Kronfeld.

Waubke, T. **Glaucomatous disposition and secondary galucoma in thrombosis of retinal vessels.** Klin. Monatsbl. f. Augenh. **136**:224-230, 1960.

The purpose of this study was to determine whether or not a relation exists between glaucomatous disposition and development of glaucoma after occlusion of retinal vessels. Glaucoma simplex was detected in the fellow eye in 13 out of 242 patients with thrombosis of the central retinal vein or one of its branches. Eleven out of 190 patients with central vein thrombosis had glaucoma simplex in the fellow eye. In these cases only four patients had high tensions in the thrombotic eye and were considered to have true secondary glaucoma. The remaining seven patients had either subnormal, normal, or only slightly elevated ocular tension in the thrombotic eye. It was assumed that the latter group of patients actually had glaucoma simplex in the thrombotic eye, corresponding to the similar disease in the fellow eye, rather than secondary glaucoma.

The authors surmise that glaucomatous disposition does not exert significant influence on the development of secondary glaucoma after retinal vein occlusion. Tension controls of both eyes, however, are considered to be important, since in all but one out of the 13 patients with glaucoma simplex, the disease in the nonthrombotic eye was discovered incidentally during routine tension checks. (8 references, 3 figures)

Gunter K. von Noorden.

10
CRYSTALLINE LENS

Cambiaggi, A. **Studies pertaining to the nature of pseudoexfoliation of the lens capsule and its relationship to the intraocular pressure.** Boll. d'ocul. **38**:55-82, Jan., 1959.

After reviewing the literature the author presented his findings in 87 patients with pseudoexfoliation of the lens capsule. The tests performed included visual fields, gonioscopy, tonography, glaucoma provocative tests, diurnal variations of the intraocular pressure and aqueous vein studies. Histologic studies were also made of pieces of iris and lens which had been removed at the time of surgery. The author concluded that while there is a statistical relationship between pseudo-

exfoliation of the lens capsule and glaucoma and cataract formation, the glaucoma seen in patients with pseudoexfoliation of the lens capsule is not secondary to the capsular exfoliation. (2 figures, 3 graphs, 3 tables, 63 references)

Joseph E. Alfano.

Papapanos, G. and Schenk, H. **The results of cataract surgery during the first ten years of life.** Ophthalmologica **139**: 62-75, Jan., 1960.

This is a ten-year follow-up study of patients who had had cataract surgery performed on one or both eyes before the age of 10 years. The patients, or rather their eyes were divided into three groups: 1. congenital cataract due to fetal iridocyclitis, 2. congenital cataracts due to metabolic diseases of the mother or due to heredity and 3. traumatic cataracts. In patients of group 1. the authors find that the ultimate vision, irrespective of the time of the operation, rarely exceeds 3/60. The operations in these patients should therefore not be performed before the age of 4 or 5 years. Total congenital cataracts of both eyes without any signs of an inflammatory process should be operated on during the first year of life. The most favorable time for partial cataracts which are not inflammatory in origin is again the fourth or fifth year of life. Traumatic cataracts in children, as in adults, should not be operated on any earlier than one year from the time of injury. (4 tables, 23 references) Peter C. Kronfeld.

Quaranta, C. A., Tedechi, L., Tittarelli, R. and Vozza, R. **Effect of hypoglycemic sulphonamides on diabetes.** Boll. d'ocul. **38**:41-55, Jan., 1959.

The paper is divided into two portions: the first deals with the action of D860 on experimental diabetes in rabbits, and the second with the retinal changes produced in rabbits made diabetic by the injection of dithizone. The authors found that the administration of D860 (N-4 methylbenzosalphony N'buthylurea) to rabbits in which diabetes had been induced was followed by a persistent lowering of the blood sugar and a delay in the onset of the appearance of lenticular opacities as well as a delay in their progression. They also observed that the retinal lesions which were produced in eyes of rabbits made diabetic by the injection of dithizone were probably of a toxic nature and therefore independent of the severity of the diabetes. (2 tables, 14 references)

Joseph E. Alfano.

11
RETINA AND VITREOUS

de Deus, F. and Faria, J. **The pathogenesis of hypertensive retinopathy.** Rev. brasil. oftal. **19**:45-52, March, 1960.

After studying venous pressure and its measurement, the authors correlate the values which they found for arterial hypertension and venous pressure and conclude that elevation of the venous pressure constitutes a prognostic factor in the occurrence of hypertensive retinopathy. (4 tables, 21 references)

Walter Mayer.

Elliott, A. J. **Lesions of the macula and perimacular region of involutional and senile origin.** Michigan St. M. Soc. J. **58**: 2002-2006, Dec., 1959.

Elevated and non-elevated lesions of the macula are reviewed and illustrated in the light of the author's own experience The conditions discussed include tumors, vascular changes, hypersensitivity states, and trauma. (14 references)

Edward U. Murphy.

Malbrán, E. and Dodds, R. A. **Scleral buckling with circling polyethylene tube.** Arch. oftal. Buenos Aires **34**:306-309, Nov., 1959.

This operation was done on 45 patients

with retinal detachment (detachment with large or multiple breaks, or with fixed folds; detachments with high myopia or aphakia; cases of badly retracted vitreous, or secondary to the extraction of an intraocular foreign body). Of these, 21 (47 per cent) were cured, and six (13 per cent) improved; in the remaining 18 cases (40 per cent) no amelioration occurred. (10 references)

A. Urrets-Zavalía, Jr.

Tittarelli, R. **X-ray therapy of occlusions of the central retinal vein.** Ophthalmologica **139**:119-133, Jan., 1960.

In 1957 Bangerter and Hohl introduced a new technique of administering X rays to the posterior segment of the eye. The patient's head is accurately fixed, his eyes directed straight downward and a lead contact lens inserted to shield the anterior segment of the eye to be treated. In that position the posterior segment may be reached by an X-ray beam that just clears the upper and temporal orbital rim. To combine large doses to the region of the disc with minimal disturbance of the overlying tissues the X-ray tube is made to swing in a plane subtending an angle of 45 degrees with the floor of the orbit. In this plane the tube describes pendulum-like movements of about 180 degrees excursions, remaining directed at the region of the disc ("pendulum-convergence-irradiation").

The total dose in cases of venous occlusion is 700-1500 r, administered in individual doses of 150-200 r (250 KV, 2.9 mm. copper filter, at a distance of about 50 cm.).

Fourteen cases of main-stem occlusion and 15 cases of branch occlusion were treated in this manner. In seven cases the X-ray therapy was combined with anticoagulants. The author describes the results as in general very good, in terms of regression of the fundus changes and of recovery of central vision. No complications attributable to the radiation were noted during the follow-up period of one year. (8 figures, 3 references)

Peter C. Kronfeld.

Wagner, K. and Conrads, H. **Histologic study of a case of retinal periphlebitis.** Ophthalmologica **138**:399-405, Dec., 1959.

Without reference to history or clinical findings the author describes the pathologic changes in the retina and in newformed pre-retinal tissues in a case of retinal periphlebitis and interprets them as tissue responses to an anaphylactic process. (4 figures, 12 references)

Peter C. Kronfeld.

12
OPTIC NERVE AND CHIASM

Dorello, U. and Scardovi, C. **The eye and the sinuses.** Riv. oto-neuro-oftal. **34**: 522-543, Sept.-Oct., 1959.

The authors' investigation of 279 patients with abnormality of the optic nerve lead them to believe that there is a relationship between disease of the sinus and the lesion in the optic nerve in a significant percentage of cases. They therefore advise that a thorough study of the paranasal sinuses be carried out in all cases of inflammatory disease of the optic nerve. (8 figures, 48 references)

Wm. C. Caccamise.

NEWS ITEMS

EDITED BY DONALD J. LYLE, M.D.
411 Oak Street, Cincinnati 19, Ohio

News items should reach the editor by the 10th of the month. For adequate publicity, notice of postgraduate courses and meetings should be received three months in advance.

DEATHS

Eugene Leslie Christensen, Los Angeles, California, died March 22, 1960, aged 61 years.

Wade Hampton Miller, Kansas City, Missouri, died March 13, 1960, aged 65 years.

Charles Edward Savery, Deerfield Beach, Florida, died February 13, 1960, aged 71 years.

ANNOUNCEMENT

CONTACT LENS TECHNICIANS TRAINING PROGRAM

To train competent and ethical technicians who will be available to the ophthalmologist either under the employment of the ophthalmologist or working independently but available to patients of ophthalmologists, The Ohio State University, Department of Ophthalmology, Columbus 10, Ohio, is offering a training program for contact lens technicians. The duration of the course is six months (with a three-week probationary period). Male students with two years of college training or its equivalent are preferred. The cost is $300 for the term.

Preceptor type of training, given in the contact lens clinic, includes the fitting and adjustment of lenses on patients. Students attend basic science lectures (anatomy, optics, physiology, and so forth) with orthoptic students. A certificate will be issued upon satisfactory completion of the training. The next course starts October 1st. For further information write Dr. William H. Havener, Department of Ophthalmology, The Ohio State University, Columbus 10, Ohio.

SEMINAR ON GLAUCOMA

A seminar on glaucoma with particular emphasis on gonioscopy and the study of the anterior angle will be given at the Brooklyn Eye and Ear Hospital on November 14th, 15th, and 16th. Ample opportunity for practical instruction in the use of the gonioprism will be given and material from the glaucoma clinic will be utilized. The course will be given by Dr. Daniel Kravitz, assisted by Drs. Nicholas P. Tantillo and Samuel Zane. Registration is limited to six (6) ophthalmologists. Application and the fee of $50.00 may be addressed to: Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Avenue, Brooklyn 38, New York.

COURSE ON CORNEAL SURGERY

A concentrated course in corneal surgery will be given under the direction of Dr. A. Benedict Rizzuti at the Brooklyn Eye and Ear Hospital on Thursday, Friday and Saturday, November 17th, 18th, and 19th.

Present surgical concepts of kerectectomies and keratoplasties will be stressed. Allied subjects, such as beta radiation, contact lenses, operating room photography, instrumentation, and so forth will be discussed by staff members. Surgical procedures in the operating room will be demonstrated according to availability of donor material. Participants will be offered an opportunity to apply surgical principles on animal eyes.

The course is limited to six ophthalmologists, tuition is $100.00. Address inquiries to Mr. Henry Williams, superintendent, Brooklyn Eye and Ear Hospital, 29 Greene Avenue, Brooklyn 38, New York.

SURGERY COURSE AT EMORY

A postgraduate course in "Techniques in ophthalmic surgery" will be presented on December 1st and 2nd, at the Grady Memorial Hospital, Atlanta, Georgia, under the sponsorship of the Grady Clay Memorial Eye Clinic and the Department of Ophthalmology of the Emory University School of Medicine.

The course is designed for the practicing clinical ophthalmologist and will consist of lectures and panel discussions by such outstanding national authorities as Dr. Frank Costenbader, chairman, Department of Ophthalmology, Children's Hospital, Washington, D.C.; Dr. John McLean, professor of ophthalmology, Cornell University School of Medicine, New York; and Dr. Harold Scheie, professor of ophthalmology, University of Pennsylvania School of Medicine, Philadelphia.

Diagnostic principles and techniques, preoperative and postoperative management, and surgical principles and techniques in extraocular muscle surgery, cataract surgery, and glaucoma surgery will be discussed by these distinguished surgeons. For further information write to Dr. F. Phinizy Calhoun, Jr., Department of Ophthalmology, 80 Butler Street, S.E., Atlanta 3, Georgia.

MISCELLANEOUS

LESLIE DANA AWARD

The Leslie Dana Gold Medal Award for meritorious work in the field of sight conservation and prevention of blindness was recently presented to Dr. Derrick Vail of Chicago. The presentation was made by Dr. Leslie C. Drews, Saint Louis, a member of the executive committee of The Lighthouse for the Blind and The St. Louis Society for

the Blind at a dinner which was jointly sponsored with the St. Louis Ophthalmological Society.

Dr. Vail is the 34th recipient of the Award since it was established in 1925 by the late Leslie Dana, who was a prominent business man of Saint Louis, Missouri.

A member of the board of directors of the Illinois Society for the Prevention of Blindness, Dr. Vail is past president of the American Ophthalmological Society, the American Academy of Ophthalmology and Otolaryngology and of the American Board of Ophthalmology.

Royal Society

Among the 25 recently elected fellows of the Royal Society in Sir Stewart Duke-Elder, ophthalmic surgeon and director of research, Institute of Ophthalmology, the University of London.

Albert C. Snell Lecture

The Fifth Annual Albert C. Snell Memorial Lecture was given on April 14, 1960 by Dr. David G. Cogan, professor of ophthalmology and director of Howe Laboratory, Harvard Medical School. He spoke on "Visual and paravisual symptoms of cerebral disease." An afternoon clinic was held at the University of Rochester School of Medicine, and Dr. Cogan's lecture followed a dinner in the evening.

Societies

Montreal lecture

Dr. Gordon M. Bruce, professor of clinical ophthalmology, College of Physicians and Surgeons, Columbia University, New York, will be the guest speaker at the fall meeting of the Montreal Ophthalmological Society, being held at the Royal Victoria Hospital, Montreal, on Wednesday evening, November 2nd. The title of his address is "The A-V syndromes." Papers by society members will complete the program.

AOS officers

At the recent meeting of the American Ophthalmological Society in Colorado Springs, the following officers were elected for the coming year: President, Dr. Edwin B. Dunphy, Boston; vice-president, Dr. Francis H. Adler, Philadelphia; secretary-treasurer, Dr. Joseph A. C. Wadsworth, New York; editor of *Transactions*, Dr. M. Elliott Randolph, Baltimore; program chairman, Dr. Frank W. Newell, Chicago.

Personal

Dr. Jack P. Cowen, Chicago, will present a paper before the Tokyo Ophthalmological Society and the Keio University in October. The subject will be "Pool gonioscopy: Technique and visualization of the anterior chamber of the eye."

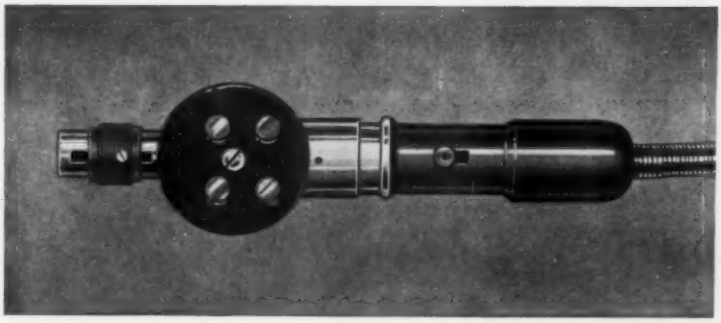
CONTENTS

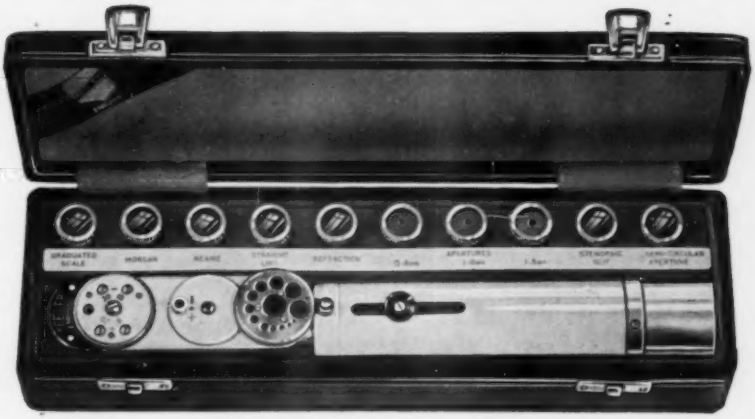
(Continued from page xxxix)

Instruments Old & New

The KLEIN KERATOSCOPE featured alongside is one of the recently introduced additions to the Keeler range.

Below are featured two old favorites, the Keeler 4-Dot Focal Illuminator, and the Keeler "Measuring" Ophthalmoscope.





For full details of the above, or any item of the Keeler range please write.

KEELER OPTICAL PRODUCTS, INC.

5536 Baltimore Avenue, Philadelphia 43, Pa.

GRanite 4-5310 - Telephones - Kingswood 4-0874

AMBROSIA... DEVILISH OR DIVINE?

To most, AMBROSIA signifies "food for the Gods"..."divine"..."particularly delicious"— at least something pleasant. But, ambrosia also stands for ragweed — of not such divine significance to allergic patients. However, the ocular symptoms of most patients reacting to genus ambrosia *(and other allergens) can be controlled throughout the allergy season.*

Prednefrin® 0.12% Ophthalmic Suspension

...is particularly suited for effective management of chronic allergic conjunctivitis. For these patients, PREDNEFRIN provides a specially designed formulation that:

- Checks inflammation and pain (prednisolone 0.12%)
- Improves the eye's appearance and "feel" (phenylephrine 0.12%)
- Soothes and lubricates (methylcellulose 0.12%)
- Provides prolonged action with minimal risk of irritation (the 'solution-like' suspension)

Dosage: 1-2 drops, two to four times a day.
Supply: In 5 cc. plastic dropper bottles—Rx only.

ALLERGAN PHARMACEUTICALS
Los Angeles 17, California